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INSULIN TUMOURS OF THE PANCREAS*

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IN considering insulin tumours of the pancreas it is interesting to recall the steps by which medical knowledge advanced until it became possible to diagnose these tumours, and to note what a considerable time elapsed between some of those steps. In 1869 Langerhans, while still a medical student, wrote a thesis in which he described the islands of cells scattered through the pancreas which have since then born his name. Naturally he did not guess their function. V. Mering and Minkowski in 1899 showed that diabetes mellitus could be produced in dogs by extirpation of the pancreas. In 1902 Ssobolew showed that ligature of the ducts caused atrophy of the acinar cells but not of the islets, and failed to cause diabetes. Their experimental work laid a sound foundation for the theory that diabetes was caused by the lack of an internal secretion produced in the islets of Langerhans, but in spite of many attempts by many workers, stimulated by Murray's introduction of thyroid extract in 1891, it was not until 1922 that Banting and Best isolated insulin and made it available for the treatment of diabetes. Soon after this it was found that an overdose of insulin would produce convulsions and coma associated with a low blood-sugar level, and that the prompt administration of glucose cut short these attacks. A little later cases of spontaneous hypoglycæmia were recognized (Harris, 1924), though none of Harris's three cases appear to have had insulin tumours, if one may judge by their symptoms; and occasionally pathologists described tumours of islet origin. It was not until 1927 that Wilder, Allan, Powers, and Robertson (1927) reported a case of hypoglycæmia due to a malignant islet-cell tumour which was verified by operation. In 1929 Roscoe Graham excised the first insulin adenoma and cured his patient, though the growth was suspected of malignancy (Howland, Campbell, Maltby, and Robinson, 1929). Since then something over 400 cases of insulin tumours have been reported, of which roughly 90 per cent have been benign and 10 per cent malignant.

As the main interest of these tumours lies in their diagnosis, I will describe the clinical histories of 5 cases of benign insulin adenoma that I have had under my care, with one dubious case and one case of malignant insulin tumour.

CASE REPORTS

Case 1.—Mrs. A. M., aged 33, was referred to me from the Neurosurgical Department of the Manchester Royal Infirmary on Jan. 14, 1946, with a history of attacks of unconsciousness with rigidity in all four limbs, and periods of diplopia and amblyopia.

HISTORY.—Six months before admission she began to see double after concentrating for any length of time upon a subject. After three months of this she complained also of severe occipital headaches, and dizzy spells lasting from 5 to 10 minutes. Dizziness would be brought on by stooping. In the course of another month these attacks became more severe, and would last hours instead of minutes. The attacks would commence with profuse sweating and salivation and she would roll her eyes and grimace. Her speech was affected at first, and then she would lose consciousness for several hours. The attacks would recur twice a week, coming on when she got up in the morning. She would recover consciousness spontaneously after about half a day. At times there were periods of meaningless laughter, giving rise to the mistaken suspicion that she was drunk. In October, 1945, she was admitted to the Oldham Royal Infirmary, where a cerebral tumour was at first suspected. As investigations

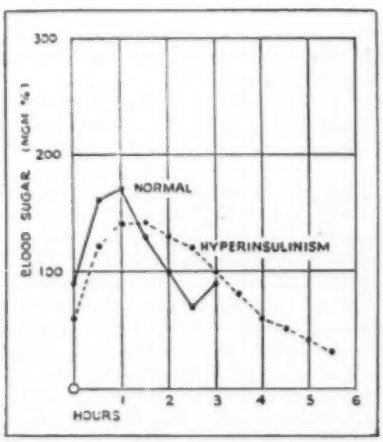

FIG. 102.—Glucose-tolerance curve in organic hypoglycæmia from insulin adenoma.

showed no evidence of this she was thought to be suffering from hysteria, and had a course of treatment by suggestion from a psychiatrist. After a fortnight of this she was advised to go back to work, but the attacks of unconsciousness returned and became more frequent and she was re-admitted to the Oldham Royal Infirmary in coma. She came round for a few hours, but on Nov. 29, 1945, was admitted to the Neurosurgical Department of the Manchester Royal Infirmary in coma from which she could not be roused at first by pressure on the supra-orbital nerve. Neurological examination revealed no evidence of a focal lesion, but it was thought that she

* The paper comprises the major part of a Litchfield Lecture delivered at the Radcliffe Infirmary, Oxford, Feb. 6, 1952.

might have a cerebral tumour in a silent area. With the object of reducing any cerebral œdema she was given hypertonic glucose intravenously, when she promptly recovered consciousness. This roused the suspicion of an insulin adenoma for the first time. Her fasting blood-sugar was now found to be 58 mg. per cent, and the glucose-tolerance curve typical of organic hypoglycæmia (*Fig.* 102). No evidence of pituitary or hepatic dysfunction was found, and it was concluded that she must have an insulin adenoma of the pancreas.

I operated on Jan. 18, 1946, under spinal anæsthesia, with intravenous glucose running in slowly. The pancreas was exposed through a left paramedian incision. A small rounded tumour, the size of a pea, was located in the tail of the pancreas, which was excised to ensure

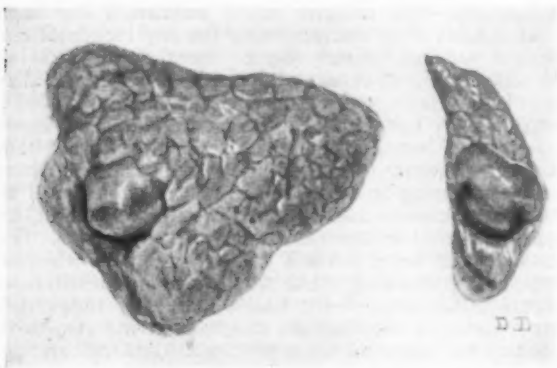

FIG. 103.—Tail of pancreas containing tumour removed from *Case* 1.

complete removal of the tumour (*Fig.* 103). The next morning the blood-sugar was 241 mg. per cent and the glucose drip was stopped.

Professor S. L. Baker reported that the encapsuled tumour consisted of irregular strands of small cells resembling those of the islets in the adjacent pancreatic tissue.

The patient made an uneventful recovery and her glucose-tolerance curve became normal. Ten days after the operation the House Surgeon wrote: "It is very remarkable how this patient's whole mentality has changed since the removal of the tumour. Instead of the rather surly, sulky-faced woman of the low blood-sugar, she is quite a happy, cheerful, smiling individual."

She has remained quite free from attacks and in normal health since. Just over a year after the operation she had a baby after a normal pregnancy, and is at present going out to work all day and running her house and feeding her family in her off time.

Case 2.—Mrs. D. S., aged 38, a clerk, was admitted to the Manchester Royal Infirmary in coma on July 8, 1946, under the care of Dr. Hillyard Holmes. The history obtained from her friends was that six months before she began to complain of frequent and severe headaches, with numbness of her tongue. These had continued since. A month before admission she had an attack of prolonged meaningless laughter followed by a drowsy state. She was in bed in an apathetic condition for ten days and then recovered and returned to work. The day before admission she began to feel drowsy and became quite unconscious in an hour or two. Towards evening she revived a little and had another period of meaningless laughter, after which she became drowsier. On the day of admission she began to shout and clutch her throat and went blue for a few minutes. She then relapsed into coma, which persisted up to her admission. She showed some response to pressure on the supra-orbital nerve.

The impression of the Registrar admitting her was that the diagnosis lay between cerebral tumour, subdural hæmatoma, and hypoglycæmia. Her fasting blood-sugar was found to be 10 mg. per cent, and blood-urea 30. The C.S.F. was normal except that its sugar content was low. Neurological examination revealed no evidence of an organic lesion in the central nervous system. Glucose was administered by a Ryle's tube and by intravenous drip, and the patient recovered consciousness quickly, but remained irritable and not very co-operative. Two days after admission her fasting blood-sugar was 48 mg. per cent.

She was transferred to my wards and on July 19 I explored her pancreas. A small firm encapsuled tumour, purple in colour, was palpated in the tail of the pancreas, which was excised as in *Case* 1.

Her convalescence was delayed by a pancreatic fistula and some sepsis in the wound, but her blood-sugar and glucose-tolerance curve returned rapidly to normal, and she has remained well since the operation.

HISTOLOGY (*Fig.* 104).—Dr. Davson reported: "The neoplasm is composed of epithelial cells of islet-cell type arranged partly in rounded solid masses separated by fibrous tissue strands and partly in more irregularly arranged anastomosing strands and trabeculæ separated by numerous capillaries. The nuclei of the epithelial cells are mainly round and darkly staining. The cytoplasm is eosinophilic. A very thin capsule can be made out in parts, but evidence of local invasion is present.

Case 3.—Fred H., aged 50, formerly a motor driver, now a clerk, began to suffer from 'fits' nine years before admission. They recurred at first at intervals of six months, and he had been regarded for the whole nine years as an epileptic and treated with epanutin. For the past five years the fits had become more frequent and for the last twelve months had occurred first at fortnightly intervals and latterly three times a week. They generally came on about 6 or 7 a.m., but occasionally during the day. The attacks were preceded by blurred vision,

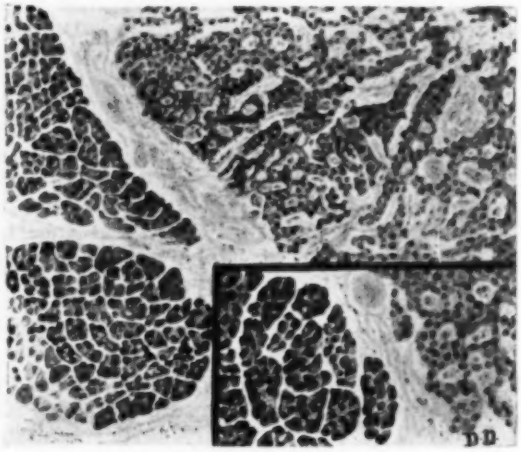

FIG. 104.—Showing structure of insulin adenoma in *Case* 2 contrasted with normal pancreas.

inability to concentrate, loss of memory, and a sensation of heaviness in his head. These symptoms lasted from ten minutes to half an hour and he would then become unconscious for from one to three hours. He had noticed five years before that he tended to get an attack if he missed a meal, and could ward them off by frequent meals. He carried chocolates with him for this purpose. In severe attacks he would be violent and restless, throwing his arms about and sustaining bruises. He had never bitten his tongue or been incontinent of urine or fæces.

On Nov. 3, 1948, he had a very severe attack and was admitted unconscious to Bury Infirmary. Here it was found that the 'fits' became more frequent. He told the house surgeon that whereas in hospital his last meal was at 6.30 p.m., at home he had been in the habit of taking supper at 10 p.m. and this led to a blood-sugar estimation.

He was observed in an attack in Bury Infirmary, when he became violent, lashing out with his arms, sweating profusely, and frothing at the mouth. He was also slightly cyanosed and showed twitching and convulsive movements very like epilepsy, but was never incontinent. His fasting blood-sugar was 33 mg. per cent.

He was seen by Professor T. H. Oliver and transferred to his wards at the Manchester Royal Infirmary on Nov. 18. Here the low fasting blood-sugar was confirmed and the glucose-tolerance curve was found to be typical of organic hypoglycæmia. Neurological investigations were negative, and the liver function tests gave normal results.

OPERATION (Nov. 29).—A transverse incision was made dividing both rectus muscles just above the subcostal plane. The gastrocolic omentum was divided transversely, thus opening the lesser sac freely. The second part of the duodenum and head of pancreas were then mobilized. A small nodule overlying the head of the pancreas, reddish in colour, was excised and sent for section, but it proved to be a normal lymph-gland. On mobilizing the body and tail of the pancreas a small, firm, rounded tumour (*Fig.* 105) could be felt in the substance of the tail. This part was excised as in the previous cases, but in this manœuvre the splenic artery was divided. This necessitated removal of the spleen as well.

Five per cent glucose was given intravenously during and after the operation, and the blood-sugar recorded every two hours.

The patient made an excellent recovery. He had no more attacks, in spite of fasting 9 and 12 hours on different occasions, and the glucose-tolerance curve eleven days after operation was normal. On April 9, 1949, five months after the operation, blood-sugar after 12 hours' fasting was 109 mg. per cent. He reported two years after the operation that he had had no more 'black outs' and has remained perfectly well since the tumour was removed.

FIG. 105.—Tumour removed from *Case* 3.

HISTOLOGY.—Dr. J. Davson reported: (*a*) An encapsuled islet tumour. The epithelial cells have fairly abundant eosinophilic cytoplasm and are arranged in a network of anastomosing trabeculæ in some areas, and in other areas form a continuous syncytium in which a slight tendency to acinar arrangements can be detected. In one area the capsule has been breached: The appearances suggest local malignancy. (*b*) The lymph-node is free from secondaries.

Case 4.—Kenneth D., aged 28, a toy dealer by trade—an obese man weighing 14 st. 11 lb.—was referred to me by Dr. Noman Kletts. For three years he had suffered from attacks that had been regarded as petit mal. During these attacks he would throw his arms about and become mentally confused and amnesic, but had only lost consciousness completely on two occasions, once for about 10 minutes and once for 45 minutes. He had headaches after the attacks. He had never injured himself or had

FIG. 106.—Multiple tumours in resected body and tail of pancreas from *Case* 4. The isolated tumour was enucleated from head of pancreas.

incontinence of urine in the attacks, and between the 'fits' he felt well. He had noticed that if he missed a meal he tended to have an attack, and they never came on within 2 hours of a meal. He had made a habit of taking lumps of sugar in his pocket to ward off an attack.

His wife stated that when an attack was coming on he looked pale and felt faint. He would sweat profusely and his speech became blurred as though he were drunk. He would be shaky all day after an attack. If driving a car when hungry he was unable to drive straight. During the fits he was never violent or excited, but his manner was slow and stupid, and to other people he appeared 'silly'. He would move his hands and arms about aimlessly like a baby. Phenobarbitone tablets would not stop the fits, but a drink of sweetened coffee would.

He was admitted to the Manchester Royal Infirmary on Sept. 19, 1949. His blood-sugar was 33 mg. per cent after fasting for 18 hours, which brought on a typical attack. Neurological examination was negative and his liver function was normal.

OPERATION (Oct. 4).—A transverse incision was made in the subcostal plane dividing both recti. The pancreas was explored in the usual way by mobilizing the second part of the duodenum with the head of the pancreas, and by opening the lesser sac widely through the gastrocolic ligament. Five rounded or oval tumours, some the size of walnuts and some smaller, much harder in consistency that the surrounding pancreatic substance, were readily palpated. One was in the head of the pancreas. This was enucleated with some difficulty. The others occupied a great part of the body and tail. They were removed by resecting the whole of the body and tail of the gland (*Fig.* 106). Access was most difficult on account of his obesity, and the resection had to be carried out largely by touch. Suture of the divided pancreas just to the left of the neck was difficult and not very satisfactory. There was some trouble from bleeding during the operation. A drain was inserted at each

extremity of the wound down to the pancreas. A blood transfusion of 2 pints was given after the operation. On the second day he developed a paralytic ileus, which was treated by gastric suction and intravenous glucose-saline and settled in three days. He then developed a profuse pancreatic fistula and later an abscess in the subhepatic fossa, with a swinging temperature. This responded to treatment by streptomycin. After a slow and tedious convalescence he returned home on Jan. 13, 1950, with the wound almost healed. After the operation there was a short period of hyperglycæmia requiring treatment by insulin, but his blood-sugar soon settled down to normal.

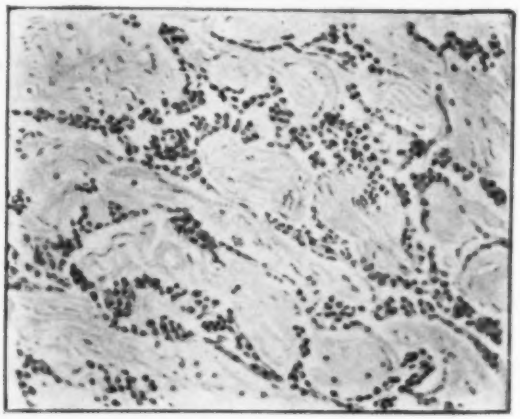

FIG. 107.—Structure of a tumour in *Case* 4.

PRESENT STATE.—He reports that when he went home he gradually improved. There have been no further attacks such as he had before the operation.

HISTOLOGY.—Dr. Parkes reports as follows on three of the adenomata: (*a*) A thick fibrous-walled cyst 2 cm. in diameter surrounded by slightly compressed normal pancreas and lined with tumour tissue. The tumour consists of sheets and anastomosing cords of basophilic cells in intimate contact with the thin-walled capillaries. The cells are mainly polygonal, but the layer adjacent to the capillaries is columnar. The nuclei are round, pale, and vesicular, and there are few irregularities of size. No mitoses were seen. (*Fig.* 107.) There are areas in which the cytoplasm of the tumour cells is swollen and undergoing hydropic degeneration. The nuclei of these cells are irregular in outline and density. There is no invasion of blood-vessels or other evidence of malignancy. At several points the capsule contains some tumour cells, but this appearance is probably due to the irregularities of the capsule and is not true infiltration. (*b*) A nodule of tumour 2 cm. in diameter similar to that of the cyst, except that there are many small areas of hyaline change in the thickened collagenous walls of the capillaries. The enclosing fibrous capsule is thin and not well defined. (*c*) A nodule 2 cm. in diameter showing cords of tumour cells similar to those of the cyst surrounding large areas of hyaline. This tumour is not encapsulated.

These three tumours illustrate the various degrees of degeneration which commonly occur.

Tumour (*a*) is mainly cellular, with no increase of connective tissue or hyalinization, and has a thick capsule. The appearance is compatible with a young tumour arising within a fibrous-walled duct. Tumour (*b*) shows early circumpapillary increase of connective tissue and hyalinization. Tumour (*c*) shows a later stage in which the strands of tumour cells are relatively scanty and are separated by large masses of hyaline material. This tumour is not encapsulated, suggesting an origin in a terminal non-fibrous walled pancreatic duct.

Case 5.—Mr. R. C-L., aged 57, retired farmer, was referred to me by Dr. S. Almond. Seen September, 1950.

HISTORY.—In 1945 he had his first attack at the end of a hard day's work on the farm. He staggered as though drunk and became mentally confused. Another farmer who was with him and knew he had taken no drink, gave him a drink of whisky which partly revived him. Three weeks later he had a similar attack, also after a hard day's work. Three months later he had his first attack of coma. The attacks have come on with increasing frequency and for the last few months he would have several attacks a day. Two years ago his wife found that a drink of glucose would bring him round in a few minutes. The attacks would begin with irregular twitching of his limbs, most marked on the left side, and if not given glucose he would soon pass into coma, from which he could not be roused, though he would continue to kick about aimlessly with his legs.

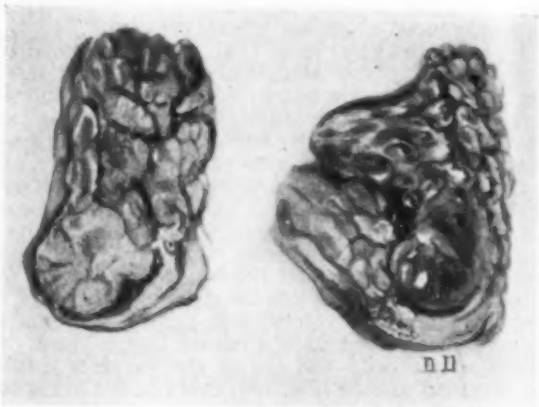

FIG. 108.—Tumour removed from *Case* 5.

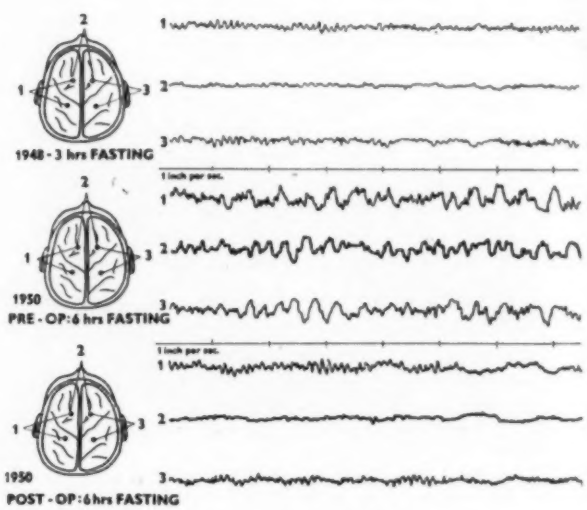

FIG. 109.—Electro-encephalograms in *Case* 5 with dates.

He had had many attacks in the night, but for the last two weeks before admission had found that if he took a large glucose drink before going to bed, they did not occur.

Two years before he was under investigation in the Private Home of the Infirmary. Insulin adenoma was

then considered, but his fasting blood-sugar was 81 mg. per cent and with the glucose-tolerance test the blood-sugar only came down to 67 mg. per cent after 2½ hours, so that diagnosis was ruled out. The blood-sugar tests were made after a few days' rest in bed, but a glucose-tolerance curve done in September, 1950, when he had not been resting, showed 44 mg. per cent after 2½ hours. After admission to the Royal Infirmary, the glucose-tolerance curve after a few day's rest in bed only came down to 73 mg. per cent in 2½ hours, but in view of the lower reading a week or two before, it was decided to explore his pancreas.

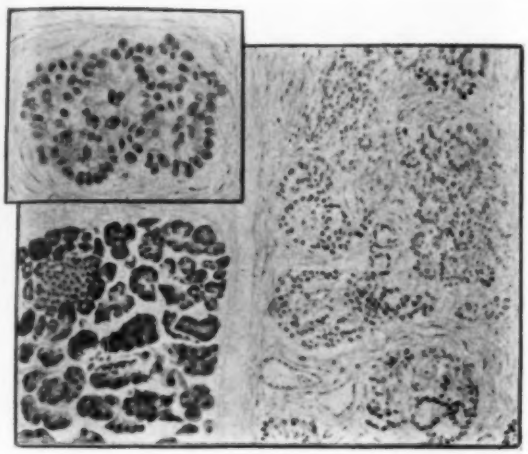

FIG. 110.—Structure of tumour in *Case* 5.

OPERATION.—Exploration was done on Oct. 10 through a transverse incision. A firm rounded nodule was found in the tail of his pancreas, which was excised. (*Fig.* 108.) The tumour was paler than some of the others, but proved to be a typical insulin adenoma. Recovery was uneventful. His fasting blood-sugar the day after operation was 241 mg. per cent and he had some glycosuria for a few days, but a week later the glucose-tolerance curve was normal.

PROGRESS.—He has remained well since and says he has lost the craving for sweet things he felt before the operation.

An electro-encephalogram before the operation showed quite remarkable cerebral commotion, but when repeated some ten days after operation it was nearly normal (*Fig.* 109).

The most interesting feature in this case is the misleading glucose-tolerance curve on two occasions after the patient had been resting in bed for a few days. The earlier of these tests delayed the diagnosis for two years. It appears to be very desirable that this test should be done when the patient is ambulant and taking some amount of exercise. It would seem advisable also to continue to make blood-sugar estimations for 5 hours after the ingestion of glucose instead of the conventional 2½ hours.

HISTOLOGY.—Professor S. L. Baker's report on the histology is as follows: "A small yellowish soft tumour about 1·5 × 1 cm. Section: An islet-cell tumour showing appearances varying from small compact cell masses to irregular strands and acinar masses of cubical or columnar cells". (*Fig.* 110.)

I must mention a sixth case that is more doubtful.

Case 6.—F. E. T., an air mechanic, aged 21, came under my care as a result of his telling a Wing Commander to go to hell during an interview by an R.A.F. Board. The circumstances were these: He had been training in Rhodesia as a pilot-observer, but was unable to complete the course because, though on some days his reactions were quick, on others they were dangerously slow. He had passed some very stringent tests with great credit before he went to Rhodesia, but out there found that he was very slow if he went up in the morning without any breakfast. He failed in an examination when he sat for it early in the morning on an empty stomach, though he had passed a much stiffer examination before with credit. The result was that he was grounded and sent home to train as an air mechanic. The interview I mentioned took place on his return from Africa, and while he was trying to explain to the board the medical reasons for his failure to fly, the Wing Commander kept interrupting him and brought on this deplorable breach of discipline. As a result of this incident he was referred to the station psychiatrist, who tested his blood-sugar and found that he was suffering from hypoglycæmia. He was admitted to the Manchester Royal Infirmary under the care of Professor T. H. Oliver. He complained of attacks in which he had blurred vision and an "oppressed sensation", which made him feel very stupid and lacking in energy. He also had sensations of claustrophobia at times. These symptoms were all improved by taking sugar.

His fasting blood-sugar was 50 mg. per cent, and the glucose-tolerance curve was typical of organic hypoglycæmia.

I explored his pancreas in November, 1944, but in spite of a careful search could find no tumour. Naturally his symptoms continued. Eighteen months later, inspired by some of the successful cases I have described, I explored his pancreas again, but in spite of thorough mobilization and palpation of the gland, again found no tumour. I, therefore, removed the greater part of the body and tail of the pancreas. Examination of the portion removed—at least half the pancreas—revealed no tumour, and the islands of Langerhans seemed normal in size, structure, and number. Nevertheless, in the five years since that operation, he has lost the symptoms he complained of and has carried on his work as a cotton salesman without interruption.

This was not a case of diffuse adenomatosis of the pancreas. There may have been a tiny insulin adenoma in the part removed, that eluded our search, or there may have been a purely functional element in the case.

The last case is one of the rare malignant insulin tumours:—

Case 7.—J. W., aged 73, a retired grocer, was referred to me by Dr. C. S. Don in June, 1951.

HISTORY.—This was of short duration. He had been well until the early morning of Feb. 28, 1951, when he became unconscious and only remembered coming round 12 hours later in hospital. Five weeks later he had a similar attack in the morning before taking any food. On a later occasion he missed his food for 8 hours and felt exhausted and had double vision. He said he lost consciousness for 3 hours on another occasion in the early morning, a week or two before admission to the Royal Infirmary. Attacks would usually come on after unusually severe exertion on the previous day.

A week before I saw him he had an attack which began with drowsiness. He then sweated profusely and became maniacal. His fasting blood-sugar taken at the height of this attack was only 14 mg./100 ml. He was given glucose by mouth and an hour later the blood-sugar was only 30 mg. per cent. Since then he had been on 2-hourly feeds and had kept well.

INVESTIGATIONS.—A radiograph of his skull showed absorption of the dorsum sellæ, which Sir Geoffrey Jefferson considered to be senile degeneration. The cerebrospinal fluid showed normal pressure and composition. Hepatic function tests were normal. On physical

examination the abdomen showed nothing abnormal. He was a well-nourished man and had lost only a little weight.

In view of the short history and rapid progress of his illness with the unusually profound hypoglycæmia, it was feared that his insulin tumour might be malignant, and so it proved.

OPERATION (July 10).—A transverse incision revealed a large hard malignant tumour of the tail of the pancreas, firmly adherent to the spleen and left kidney, which

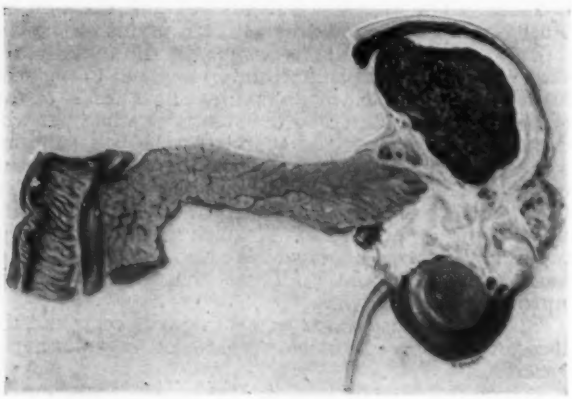

FIG. 111.—Post-mortem specimen of carcinoma of tail of pancreas infiltrating spleen and kidney in *Case* 7.

it surrounded. It was also firmly adherent to the diaphragm, transverse colon, and stomach. The tumour was plainly quite inoperable. The manipulation necessary to ascertain this caused some bleeding from the greatly engorged veins surrounding it that was difficult to control. After the operation the patient passed into coma and died in 48 hours.

POST-MORTEM EXAMINATION.—This showed a terminal thrombosis of the superior mesenteric vein and a photograph of the tumour is shown in *Fig.* 111.

Microscopical sections showed a very scirrhous tumour with small cells almost resembling lymphocytes. Professor Campbell regarded it as an unusual type of islet-cell carcinoma (*Fig.* 112).

DISCUSSION

The errors in diagnosis in my 5 proved cases of insulin adenoma are instructive. Two of them (*Cases* 3 and 4) had been regarded as suffering from epilepsy, one for 9 years and the other for 3 years. *Case* 5 had been suspected of epilepsy. In *Case* 1 the diagnosis first suggested was cerebral tumour, then hysteria, and then cerebral tumour again. In *Case* 2 cerebral tumour and subdural hæmatoma had been regarded as a possible alternative to hypoglycæmia. Three of them (*Cases* 3, 4, 5) had on occasions been suspected of alcoholic intoxication.

These insulin tumours of the pancreas are not very common, but it is probable that a good many patients suffering from them die without a diagnosis. Crain and Thorn had collected 258 insulinomas up to December, 1949, and in May, 1950, Howard, Moss, and Rhoads had collected 398. It was not until 1929, as we have seen, that Graham, of Toronto, removed an islet tumour suspected of malignancy. In 1930 Harvey Cushing removed the first definitely benign insulin adenoma.

Insulin adenomas may occur at any age, but are most common in patients between 40 and 50 years old. There is no significant difference between the sexes as regards frequency.

Number of Tumours.—It is most important that we should know what chance there is that the tumour will be single and what the prospect that it will be benign. The figures of Crain and Thorn are definite on these points. They collected 228 cases of benign adenoma against 24 malignant tumours.

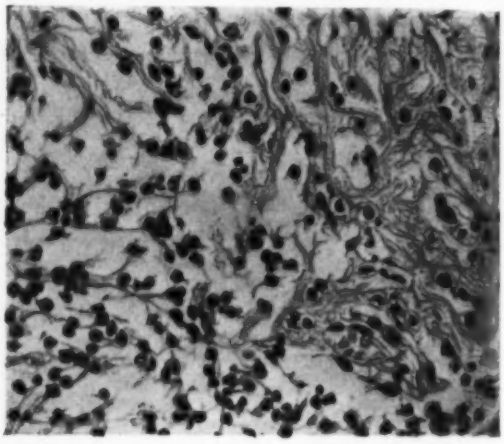

FIG. 112.—Structure of insulin carcinoma (*Case* 7).

Of the 228 benign tumours, 206, or 88 per cent, were single and only 22, or 12 per cent, multiple, and then only 2 were present as a rule. Of the 24 malignant tumours, 20 were single and 4 multiple.

There were 6 cases of diffuse adenomatosis of the pancreas.

Size of Tumours.—The great majority of tumours, 75 per cent, were between 1 and 3 cm. in

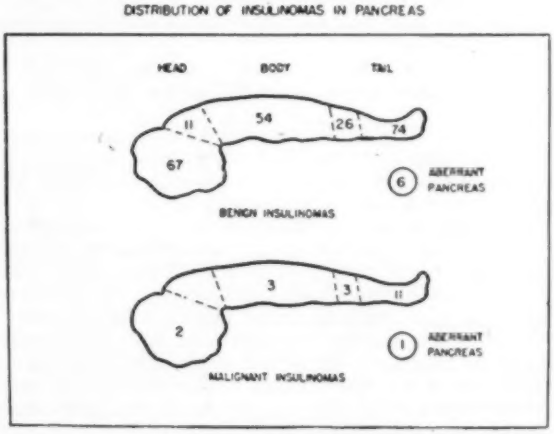

FIG. 113.—Distribution of insulin tumours. (*Reproduced from Crain and Thorn's article, by kind permission of the Editor of 'Medicine'.*)

diameter. The largest recorded was 11 cm. in diameter. It is worth noting that the size of the tumour is not significantly related to its functional activity. Some of the smallest tumours gave rise to the most profound hypoglycæmia. In my cases, the four patients who had a tiny single adenoma in the tail of the pancreas had symptoms just as dramatic as those of the man with the five adenomas.

Distribution of Tumours.—This diagram (*Fig.* 113) from Crain and Thorn shows that the tumours occur fairly evenly in the various parts of the pancreas, and not so predominantly in the tail as some authors have suggested. It must be remembered that they are much more easy to palpate in the tail than in the head or neck of the pancreas, and this may account for such preponderance as there is in this position. Nevertheless, five of my six cases were in the tail. Nine cases have been recorded of insulin tumours in an ectopic pancreas—generally in the duodenum or immediate vicinity of the pancreas (Howard and others).

Malignancy.—Although less than 10 per cent of these tumours are definitely malignant, as proved by metastases in distant parts such as the liver or lymph-glands, a considerably greater proportion have been suspected of local malignancy on the purely histological evidence that the growth had breached the capsule in one or more places. However, a number of careful 5-year follow-ups of considerable groups of such cases have shown that they do not recur or give rise to later metastases. Roscoe Graham's first case of a successful operation in 1929 came into the ' suspected malignant ' group, as would three of my five adenomas.

Duration of Pre-operative Symptoms.—Many of the recorded cases have for many years had symptoms that were finally proved to be due to hypoglycæmia. The longest on record was 20 years. My *Case* 3 had epileptiform fits for 9 years. Of the recorded cases 75 per cent have had pre-operative symptoms for over 4 years. In the comparatively rare cases of proved malignancy, the history is almost invariably under 2 years' duration.

Symptoms.—The diagnosis of these tumours is based essentially on what is now known as Whipple's (1944) triad of symptoms. These are :—

1. Nervous (or occasionally gastro-intestinal) attacks in the fasting state.
2. A fasting blood-sugar of 50 mg. per cent or lower. (In 80 per cent of cases it is below 40 mg. per cent.)
3. Immediate, or almost immediate, relief from the ingestion of glucose.

The nervous symptoms that should bring us to consider the possibility of an islet tumour are very numerous, but we may perhaps remember them best by alliteration's artful aid as beginning with the letter C. They are *confusion*, *convulsions*, *coma*, and in view of the periods of meaningless laughter in two of my cases, I would add *cachinnation*.

These patients are all too easily diagnosed as suffering from epilepsy or confusional or hysterical states, and even cerebral tumours, and run a great risk of being wrongly regarded as alcoholics. It is possible that many neurological and psychiatric clinics shelter one or more of them undetected, for they are undoubtedly more common than the published records would suggest.

There are, of course, numerous other causes of hypoglycæmia, and Sir Henry Cohen has recently given a comprehensive account of them in his Moynihan Lecture (1950). It may be stated in general terms that if a patient presents Whipple's triad of symptoms, and if gross hepatic disease or pituitary or adrenocortical deficiency can be excluded, an insulin tumour will be found in all probability. Crain and Thorn have recently described a simple subcutaneous adrenaline test which excludes anterior pituitary or adrenocortical deficiency and a subcutaneous adrenocorticotrophic hormone test which excludes adrenocortical deficiency.

Mortality.—The mortality in 200 recorded operations for this condition has been 9 per cent, and 87 per cent of patients who survived operation have been completely and permanently cured by operation. In 56 recorded cases where a tumour could not be found, partial resection of the pancreas was done, with a good result in 46·4 per cent (Howard and others, 1950).

SUMMARY

1. Five cases of benign insulin adenoma of the pancreas successfully removed by operation and one case of suspected insulin adenoma treated by subtotal resection of the pancreas are described, along with a fatal case of insulin carcinoma of the pancreas.

2. The importance of carrying out the glucose-tolerance test on the *ambulant* patient is urged, and it is suggested that the test should be prolonged for 5 hours instead of the usual 2½ hours.

3. The diagnosis of insulin tumours of the pancreas is discussed.

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TOTAL PANCREATECTOMY

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TOTAL pancreatectomy does not appear to have been successfully accomplished very frequently and the number of patients who have survived this operation for any length of time is very few indeed. From the literature we have found records of twenty-five such operations and these are listed below. There have probably been a number of other total pancreatectomies carried out which either have not been published or have escaped our notice, but in view of the paucity of the literature on this subject, and the high incidence of malignant and other disease of the pancreas in which this operation may be indicated, it was thought that it might be of value to publish details of a case which has recently been under our care.

PREVIOUSLY PUBLISHED TOTAL PANCREATECTOMIES

AUTHOR	YEAR OF OPERATION	AGE OF PATIENT	SEX OF PATIENT	DIAGNOSIS	RESULT
Priestley	1942	49	F.	Islet-cell adenoma	Alive and well 3 years after operation
Rockey	1942	51	M.	Adenocarcinoma	Died 15 days after operation
Goldner and Clark (case of Brunschwig)	1944	29	M.	Carcinoma of common bile-duct	Died 11 days after operation
Goldner and Clark (case of Brunschwig)	1944	45	M.	Carcinoma of common bile-duct	Died 10 days after operation
Brunschwig	1944	67	M.	Carcinoma	Died 3 days after operation
McClure (case of Fallis)	1944	46	M.	Carcinoma	Alive 9 months after operation
Dixon, Comfort, Lichtman, and Benson	1944	50	M.	Adenocarcinoma	Recurrence 15 months after operation
Clagett	1944	37	F.	Chronic pancreatitis with calculi	Died 3 months after operation from hypoglycæmia
Waugh	1944	36	F.	Islet-cell adenoma	Alive and well 8 months after operation
Brunschwig, Ricketts, and Bigelow	1945	53	M.	Duct-cell carcinoma	Died 3½ months after operation
Whipple	1945	26	F.	Chronic pancreatitis with calculi	Alive and well 1 year after operation
Whipple	1945	46	F.	Chronic pancreatitis with calculi	Died 7 days after operation
Zinninger	1945	39	M.	Chronic pancreatitis with calculi	Died 30 hours after operation
Brunschwig	1946	Not stated	Not stated	Carcinoma	Died 14 days after operation
Kennedy, Braitman, Marcus, Biery, and Miller	1946	43	M.	Adenocarcinoma	Died 18 days after operation
Fallis	1946	60	M.	Carcinoma	Died 6 days after operation
Gaston	1947	70	M.	Carcinoma	Died 8 days after operation
Fallis	1947	57	F.	Adenocarcinoma	Died 3 months after operation
Fallis	1948	60	F.	Adenocarcinoma	Alive and well 3 months after operation
Fallis	Not stated	Not stated	Not stated	Carcinoma	Died 18 days after operation
Fallis	Not stated	Not stated	Not stated	Not stated	Died
Waugh	1948	Not stated	Not stated	Islet-cell tumour	Survived operation
Waugh	1948	Not stated	Not stated	Chronic pancreatitis	Survived operation
Bowers	1950	Not stated	M.	Carcinoma	Recurrence evident 9 months after operation
Millar	1951	65	M.	Carcinoma	Died 48 hours after operation

CASE REPORT

Mr. T. J., aged 55, an engineer, was first seen by one of us (A. G. W. W.) on June 9, 1949. He had had no significant previous illness. For six months he had been conscious of vague ill health and at the end of April, 1949, he had had a brief attack of diarrhœa and vomiting accompanied by abdominal pain. On May 9, 1949, he had had an acute attack of abdominal pain lasting one hour. The onset and offset had been sudden and the pain had been sufficiently severe to make him "roll about". A day or so afterwards he noticed that his urine was dark and his stools pale, and though he felt ill he continued at work until one week later when he saw that he was jaundiced and retired to bed. The jaundice persisted but there had been no further pain. He was deeply jaundiced, the urine contained bile and the fæces were acholic, the liver was enlarged, and there were some petechiæ over the clavicles but there were no other abnormalities. The gall-bladder could not be felt. He was admitted to the Queen Elizabeth Hospital, Birmingham, the following day with a provisional diagnosis of stone in the common bile-duct.

A straight radiograph of the abdomen showed no radio-opaque gall-stones nor any pancreatic calcification, and a chest radiograph was clear. A barium swallow showed no œsophageal varices and a barium meal revealed no abnormality in the stomach or in any part of the duodenum. Liver function tests showed total proteins 5·3 g. per cent (serum-albumin 4·0 g. per cent, serum-globulin 1·3 g. per cent), total cholesterol 470 mg. per cent (serum-free cholesterol 210 mg. per cent, serum ester cholesterol 260 mg. per cent), serum alkaline phosphatase 17·2 units (Jenner and Kay), a positive direct and indirect van den Berg, a serum-bilirubin of 10·7 mg. per cent, a negative cephalin cholesterol, a thymol turbidity of 1·0 unit, and a two plus colloidal

gold. A blood-count was completely normal and the blood-urea was 31 mg. per cent.

AT OPERATION.—The patient was given full doses of vitamin K intramuscularly and laparotomy was carried out through a large right paramedian incision on June 18, 1949. The gall-bladder and common bile-duct were seen to be grossly distended and aspiration of the gall-bladder produced thick black bile. The whole pancreas was hard and knobbly and was thought to be malignant. No secondaries could be found in the peritoneum or in the liver, though the latter was greatly enlarged. It was decided to attempt to remove the pancreas and it was approached from above through the lesser omentum and from below by entering the lesser sac through the greater omentum. The superior mesenteric vein was defined and the pancreas eased off it above and below. The stomach was next sectioned just proximal to the pylorus and turned back. The common bile-duct was then

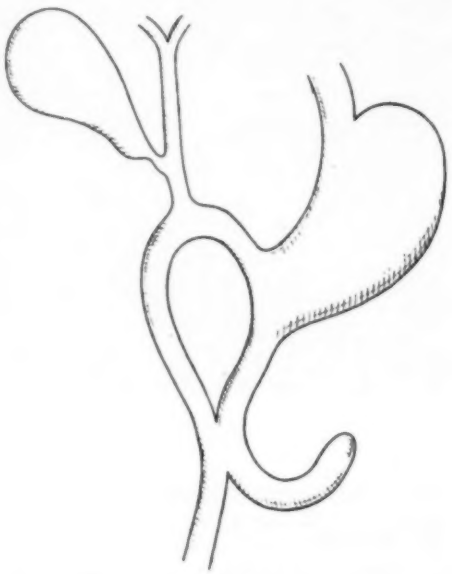

FIG. 114.—Diagram of completed first operation.

divided and the portal vein exposed. The duodenum was then mobilized from right to left, bringing the pancreas with it. A transverse incision in the abdominal wall provided access to the body and tail of the pancreas. The splenic artery was ligated and the whole pancreas, whole duodenum, and spleen were removed. As the stomach had been deprived of some of its blood-supply, about half of it was removed, a gastrojejunostomy and entero-anastomosis was carried out, and an end-to-side anastomosis was made between the common bile-duct and the jejunum (*Fig.* 114).

Histology of the pancreas revealed a papilloma near the outlet of Wirsung's duct (*Fig.* 115). Behind the papilloma the main duct was dilated and the whole pancreas showed almost complete atrophy of the acini with interstitial fibrosis (*Fig.* 116). The islets of Langerhans had survived and appeared normal (*Fig.* 117). The only healthy pancreatic tissue was a very small zone adjacent to the duodenum, which presumably drained into Santorini's duct (*Fig.* 118).

PROGRESS.—The patient stood the operation well, but his convalescence was interrupted by two small hæmatemeses on the tenth day and by rigors and pyrexia on the eighteenth and twenty-eighth days. These febrile episodes were thought to be due to ascending cholangitis and both responded immediately to the administration of penicillin and sulphonamides. He was discharged to his home two months after operation on a diet of 200 g. of carbohydrate and 75 g. of fat daily, with unlimited protein and a morning dose of 15 units of soluble insulin and 15 units of protamine zinc insulin, and 60 gr. of pancreatin three times daily.

The patient's subsequent progress was disappointing. During the 14 months following discharge from hospital he had some 17 bouts of fever, most of which were

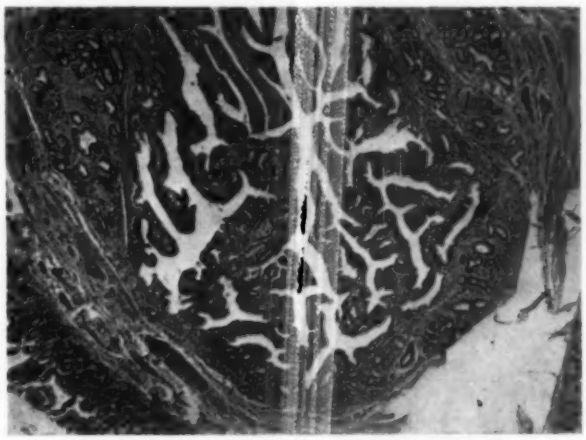

FIG. 115.—Papilloma of outlet of Wirsung's duct.

accompanied by rigors, and in some attacks there was pain under the right costal margin and the liver was enlarged and tender. Each attack resolved rapidly with penicillin and sulphonamide therapy, but the effect of these repeated cholangitic episodes was to render the patient quite unfit to return to work. Continuous administration of sulphathiazole and phthalyl sulphathiazole failed to prevent the

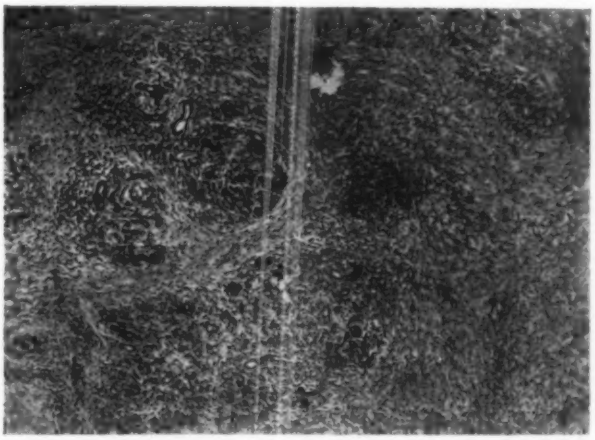

FIG. 116.—Pancreas showing atrophy of the acini and connective tissue overgrowth.

bouts of cholangitis, and our experience of another case led us to consider the advisability of performing a cholecystenterostomy in order to prevent the attacks. The patient was therefore re-admitted to hospital in October, 1950, and the gall-bladder was anastomosed to the efferent loop of the jejunum. Six months have now elapsed since this second operation and no further cholangitic episodes have occurred and the patient has felt completely normal.

Extensive investigations into the metabolic effects of total pancreatectomy have been carried out on this patient and the results of these are the subject of a separate communication—Whitfield, Gourevitch, and Thomas, 1952.

DISCUSSION

The difficulty of differentiating chronic pancreatitis from pancreatic neoplasm on the operating table is well recognized by all abdominal surgeons (Orr, 1945; d'Offay, 1946). It is in cases of chronic pancreatitis such as we have described where obstructive jaundice is the sole manifestation that such difficulty arises. The examination of a frozen section might at first sight appear to be a possible solution. That it is not so is apparent from a consideration of the pathology in this case. Here, the causative lesion, a small papilloma in Wirsung's duct, was buried beneath firm nodular pancreatic tissue. A section from this material would have shown merely the secondary pathology—i.e., the fibrotic atrophied pancreas. Had the lesion been a carcinoma of the pancreatic duct with secondary 'pancreatitis' as in another case which has come to our notice, the malignancy of the primary lesion would not have been apparent in frozen sections.

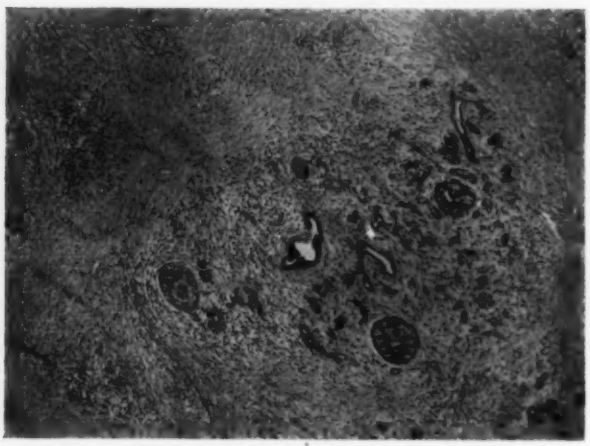

FIG. 117.—Pancreas showing survival of the islets of Langerhans.

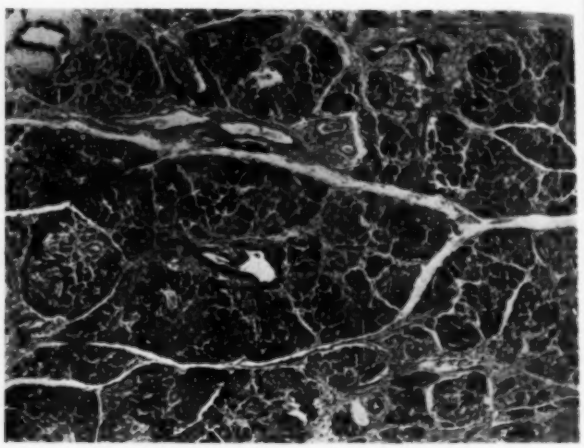

FIG. 118.—Small area of normal pancreas draining into the duct of Santorini.

The histology of the pancreas in this case was typical of the results of pancreatic duct obstruction. The dilatation of the ducts behind the papilloma at the outlet of Wirsung's duct, the atrophy of the acini, the connective tissue overgrowth, and the survival of the islets of Langerhans are all well shown, and the normality of the small area of pancreas draining through the unobstructed duct of Santorini is particularly striking. Papilloma appears to be an uncommon cause of pancreatic duct obstruction. Our case emphasizes the importance of obstruction of the pancreatic duct as a cause of generalized hardness of the pancreas. It may be that this factor has not been adequately recognized in the past and that chronic inflammatory changes have been held responsible for an organ presenting this characteristic where duct obstruction has in fact been the operative factor.

The post-operative occurrence of attacks of ascending cholangitis is of particular interest. It will be recalled that at the first operation an end-to-side anastomosis was carried out between the common bile-duct and the jejunum. The recurrent cholangitic attacks which followed this operation were eventually halted by carrying out a cholecystenterostomy. As mentioned above, the possible efficacy of this procedure was suggested by another case in which the common bile-duct was divided during a difficult partial gastrectomy for peptic ulcer and an end-to-side anastomosis was carried out between the proximal end and the duodenum. Recurrent attacks of cholangitis followed and cholecystenterostomy was performed. This procedure sufficed to prevent cholangitic attacks for a period of nine months, but they then recurred. It has been suggested that ascending cholangitis may be mediated by stricture formation at the choledochojejunal junction, but in our case of total pancreatectomy such a factor is unlikely to have been operative as the first attack occurred only ten days after operation. Removal of the protection against reflux afforded by the sphincter of Oddi seems a more likely explanation. Although ascending cholangitis is of course a common complication after anastomotic operations between the biliary and alimentary tracts, it has not been mentioned in any of the previously reported cases of total pancreatectomy. In only 10 of the 25 cases, however, was survival after operation sufficiently long for this complication to have been evident. In 6 of these 10 cases choledochojejunostomy was performed (Brunschwig and others, 1945; Dixon and others, 1946; Whipple, 1946; Fallis and Szilagyi, 1948), in 1 choledochogastrostomy (Waugh, Dixon, Clagett, Bollman, Sprague, and Comfort, 1946), in 1 cholecystogastrostomy (Priestley and others, 1944) and in 1 cholecystoduodenostomy (Waugh and others, 1946). The operative details of the remaining case were not published (Bowers, 1950).

The relatively small amount of insulin required by our patient is in accord with the experience of previous writers, most of whom were able to attain adequate stabilization on a daily dosage of 40 units or less. (Priestley, Comfort, and Radcliffe, 1944; Goldner and Clark, 1944; Waugh and others, 1946; Gaston, 1948.) Brunschwig and others (1945) reported a diabetic who after total pancreatectomy required less insulin than before operation.

Fallis and Szilagyi (1948) described a similar case, while Dixon and others (1946) reported a

diabetic whose insulin requirement after operation was only slightly greater than it had been before. These findings, and the very high insulin requirements of some diabetics, afford strong support for the current belief that there are important extra-pancreatic factors in diabetes. The literature contains numerous references to the marked insulin sensitivity of depancreatized humans, and Waugh and others (1946) described a patient who died from hypoglycæmia following total pancreatectomy. Our patient's insulin requirement was a little higher than that reported by previous writers, being of the order of 50 units daily, and insulin sensitivity was not a feature, there having been no hypoglycæmic reactions despite accurate stabilization.

SUMMARY

1. A case of total pancreatectomy is described in which the patient is alive and well twenty-two months after operation.

2. At operation the pancreas was thought to be malignant, but subsequent histology showed the lesion to be a chronic pancreatitis due to obstruction of Wirsung's duct by a papilloma.

3. The post-operative course was marred by recurrent attacks of ascending cholangitis, which were eventually controlled by cholecystenterostomy.

4. The post-operative insulin requirement was about 50 units per day.

We are greatly indebted to Professor J. W. Orr for the histology in this case and for providing the microphotographs. Our thanks are also due to Mr. T. F. Dee for reproducing *Fig.* 114, and to Mr. Garfield Thomas for conducting the biochemical investigations.

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THE SURGICAL MANAGEMENT OF THE PENETRATING POSTERIOR WALL DUODENAL ULCER

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THE Billroth II type of partial gastrectomy is now one of the standard operations of surgery, and in a skilled surgical organization it carries a low mortality. The risk of operation no longer greatly depends upon the state of the patient, for with adequate preparation, skilful anæsthesia, precise surgery, and knowledgable post-operative management, it is possible to operate safely even on the many ill patients who require surgical treatment. The hazard lies rather in the technical difficulties surrounding the duodenal stump, and the mortality-rate of a large series of gastrectomy operations will largely depend upon the proportion of grave anatomical and pathological problems encountered around the duodenum, and the skill and experience with which they are met.

The most serious difficulties arise from the ulcer of the posterior duodenal wall which has penetrated into the pancreas and there formed a callous ischæmic ulcer crater. If the ulcer is within 1–2 cm. of the pylorus it is usually possible to mobilize the posterior duodenal wall distal to the ulcer and obtain safe 'two-layer' closure in a healthy portion of duodenal wall; but when the ulcer involves the duodenal wall and pancreas more than about 1 cm. to the right of the line of the gastroduodenal artery, the risk of injury to bile or pancreatic ducts is grave if an attempt is made to free the posterior wall of the duodenum for even a short distance distal to the ulcer crater.

The reason for this hazard does not lie in too slender an acquaintance with the anatomy of the region or simply in the difficulty of recognizing anatomical structures in the œdematous scarred tissue of duodenal wall and pancreas. Even when it is understood that anatomical abnormalities in the arrangement of bile and pancreatic ducts are so common that no 'normal' anatomy can be expected, it has still to be learned that as a result of tissue destruction and scar contraction these important ducts can lie in places where they have no reasonable right to be! Such an instance is illustrated in *Fig.* 119.

When at operation the duodenum was divided proximal to a penetrating chronic ulcer of the first part of the duodenum not only was a deep excavation into the pancreas revealed, but immediately beyond the distal edge of the crater the ampulla of Vater presented. Although at operation the duodenum had the usual configuration of first and second parts,

sufficient destruction and contraction had occurred to pull the ducts and the mobile ampulla into this unusual and dangerous position. Clearly any attempt to mobilize the posterior duodenal wall in this case would have led to injury.

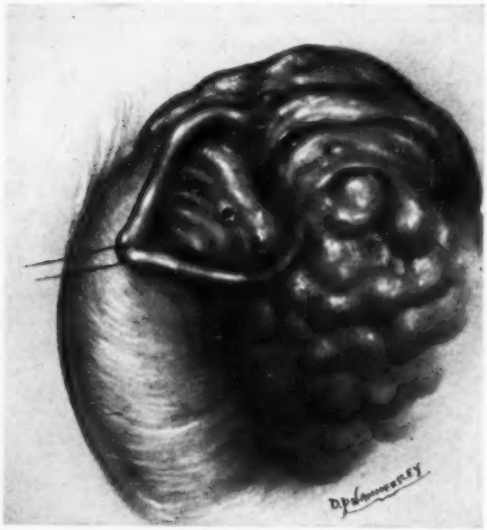
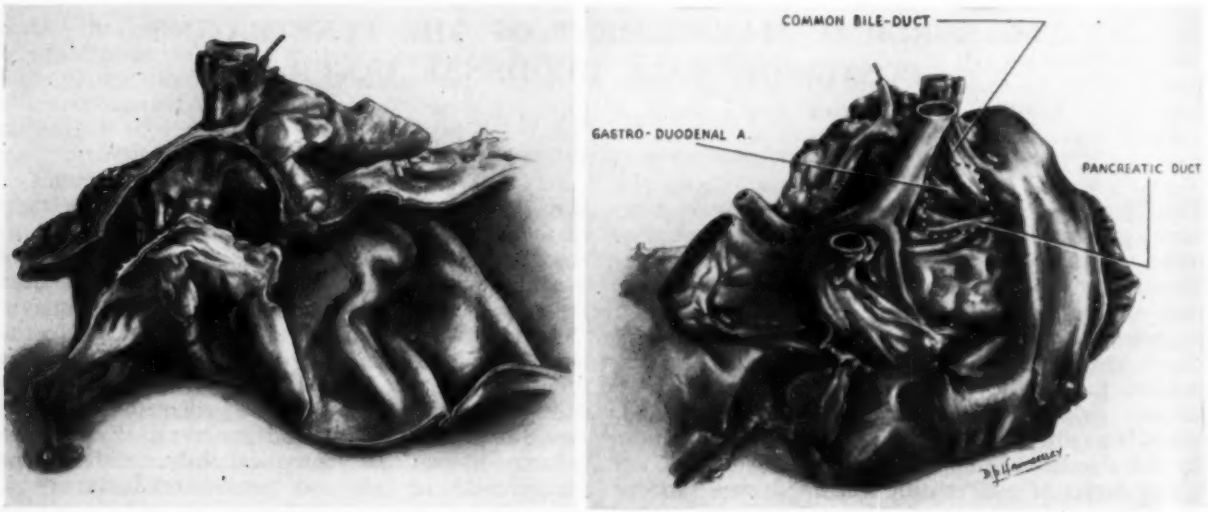


FIG. 119.—Duodenum divided at the proximal edge of a chronic penetrating ulcer in the posterior wall of the first part of the duodenum. The ampulla of Vater presents immediately beyond the ulcer crater.

A specimen removed post mortem provides another illustration of the same danger. The patient died from a massive hæmorrhage from perforation of the gastroduodenal artery in the base of a chronic ulcer of the first part of the duodenum. Dissection of the ducts demonstrated that the edge of the common bile-duct had come to lie against the gastroduodenal artery behind the ulcer crater, and that the artery was crossed by the pancreatic duct also in relation to the ulcer floor (*Fig.* 120). If operation had been attempted any dissection of the posterior duodenal wall in the region of the ulcer would have been disastrous.

It is sometimes held that these hazards may be avoided by opening the common bile-duct in the lesser omentum and passing a bougie down the duct into the duodenum, so defining precisely its course and making easy the necessary avoiding action. Incision and subsequent drainage of the bile-duct adds, however, to the morbidity of the operation and increases the delay of convalescence; more importantly, although it safeguards the common duct, it does nothing to ensure the safety of a pancreatic duct which enters the duodenum separately from the common bile-duct—as for instance into the posterior aspect of the first part of the duodenum. Such an occurrence which led to a fatal pancreatic leak is illustrated in *Fig.* 121. At operation a deep penetrating ulcer was found in the line of the gastroduodenal artery which was perforated and bleeding. A cuff of posterior duodenal wall was raised from the œdematous pancreatic scar for nearly 1 cm. distal to the line of the artery, the vessel tied, and the duodenum closed. A pure pancreatic fistula followed, from which the patient died (by erosion into the splenic artery); the post-mortem specimen revealed a healed duodenal stump and the orifice of a large pancreatic duct opening on the surface of the pancreas just distal to the site of the original ulcer (*Fig.* 121).

It is probably true to say that as the experience of a surgeon in ulcer surgery increases, the desire to disturb the posterior duodenal wall distal to the edge of a deep chronic ulcer into the pancreas decreases; and that in the presence of such an ulcer with gross surrounding œdema and scarring, the post-duodenal area can be regarded as a region without an anatomy—and one to be avoided.



A B

FIG. 120.—Dissected specimen, removed post mortem. A, Anterior view of a chronic penetrating ulcer in the posterior wall of the first part of the duodenum, showing perforation into the gastroduodenal artery. B, Posterior view of the same specimen. The dotted line indicates the limits of the ulcer base. The common bile-duct and the pancreatic duct lie behind the ulcer floor.

SURGICAL MANAGEMENT

The problem at operation may present and be solved in different ways :—

1. Division and Closure of the Stomach or Duodenum.—When the existence of a large penetrating posterior ulcer is recognized early in the operation, as by the presence of a mass or extensive induration in the head of the pancreas behind the first part of the duodenum, a decision can be made to divide the gut proximal to the ulcer without disturbing or dissecting the ulcer site, always providing that the operation is one of election and is not for uncontrolled bleeding. The choice between division of the pyloric antrum 5 cm. to 6 cm. proximal to the pylorus, and section of the duodenum distal to the pylorus but proximal to the ulcer, will depend on obvious local circumstances—the site of the ulcer, the condition of the duodenal wall, the degree of œdema, and the extent of glueing of the structures of the right upper abdomen into a continuous inflammatory mass.

Division and closure of the duodenum proximal to the ulcer, when possible, is a satisfactory operation, both immediately and late. In the 360 gastrectomies for chronic ulcer performed in this clinic since 1947, this method has been adopted 23 times. There has been no post-operative leakage and there have been no ill effects from leaving the ulcer in situ. In fact, it is clear from observations on two-stage gastrectomy (discussed below) that the ulcer heals within a few weeks of diversion of the food-channel, and is replaced by an innocent scar remnant giving no hint of its previous active inflammatory nature.

When, as sometimes happens in the presence of a large posterior ulcer, the whole duodenum is involved in solid œdema, and particularly when it forms part of an inflammatory mass in which the gall-bladder, hepatic flexure, and lesser omentum are fused, it is prudent to divide the stomach in the pyloric antrum, and either core out the mucosa by the method described by Bancroft (1932), or close the entire antral stump in preparation for a second operation to remove the stump two months later. The choice probably depends on personal predilection, amplified by one or two vivid experiences. In this clinic the preference is for a deliberate two-stage operation, for two reasons. First, closure of the entire antral wall appears in principle (and to us in practice) more safe than the method of suture permitted by the Bancroft procedure. Secondly, when the pyloric antrum too is swollen and thickened, as it may be, safe closure of the stomach wall can be more readily assured when it is divided well proximal to the inflammatory process, farther away than the Bancroft method makes feasible. The further operation, performed after 8 to 10 weeks, is remarkably simple, and the extra unpleasantness to the patient is thought to be justified by the safety of the manœuvre. To say that the two-stage operation is one for the tyro is to suggest either that the condition of severe periduodenitis has not been encountered, or its dangers not appreciated. In our series the two-stage operation has been done 11 times, with no ill effects. It is interesting to note at the second operation how completely the inflammatory process has subsided, and how much of the duodenum has sometimes been destroyed in this virulent type of ulcer process. One technical point at the first operation is worth stressing: The right gastric epiploic artery and vein should not be tied close to the lower border of the duodenum, but only near to the point at which it is proposed to divide the stomach, for the viability of the antral stump depends on these vessels. The right gastric artery and vein are often thrombosed, and even if intact are too slender to supply the whole antral wall.

2. Division and Closure of the Duodenum in the Line of the Ulcer.—The site of the ulcer or the condition of the duodenal wall may not permit duodenal closure proximal to the ulcer, while not demanding prepyloric section; or the penetrating nature of the ulcer may not be recognized at operation until the posterior wall of the duodenum is dissected and a perforation in the duodenum is uncovered; or the operation may be for urgent bleeding requiring ligature of vessels in the ulcer base. In these circumstances, in which the ulcer crater is exposed, it is possible to close the duodenum effectively without disturbing the ulcer base or attempting to free the posterior duodenal wall distal to the excavation in the pancreas. Different methods have been described; in all of them the duodenum is divided transversely or obliquely at the level of the proximal edge of the ulcer, the ulcer cavity is thus freely exposed and any bleeding vessel in the ulcer base may be underrun. The techniques of closure of the duodenal orifice are varied. Graham (1938) has described a method of exteriorization of the ulcer; Wangensteen (1940) sutures the anterior edge of the duodenal orifice to the margin of the ulcer crater in the pancreas, by interrupted mattress sutures; Yudin (1939) and Nissen (1945) infold the anterior duodenal wall into the duodenal lumen and suture it to the margins of the posterior wall ulcer with three layers of sutures. The techniques are well

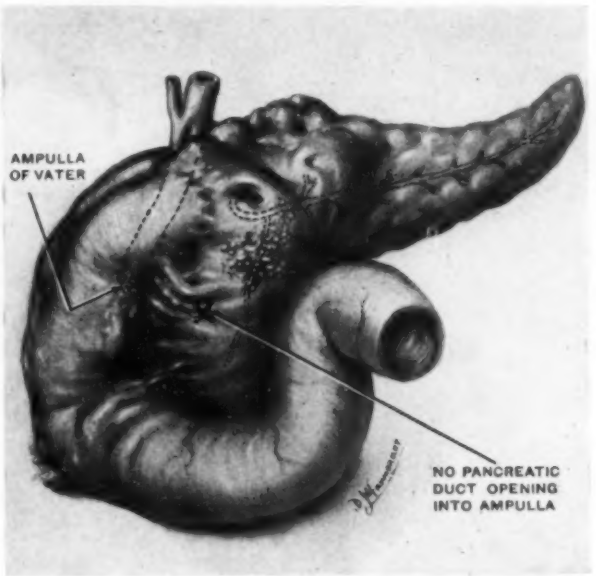


FIG. 121.—Operation had been performed for uncontrolled bleeding from the gastroduodenal artery, and a cuff of posterior duodenal wall raised from the pancreas for nearly 1 cm. distal to the line of the artery, the vessel tied, and the duodenum closed in two layers. The post-mortem specimen shows a healed duodenal stump, and the orifice of a pancreatic fistula proximal to the stump. Dissection of the specimen revealed no pancreatic duct opening at the ampulla, and showed that the main duct communicated with the fistula, and must have opened into the back of the first part of the duodenum.

illustrated in the originals, and those of Yudin and Nissen are beautifully reproduced by Maingot (1948) and Tanner (1950), and do not need repetition. All these methods require in the duodenal stump a supple mobile anterior wall, and a thick scarred edge to the posterior ulcer cavity capable of holding silk or thread sutures: conditions usually to be found in the presence of a chronic posterior penetrating ulcer.

It has seemed to me at operation when faced with this problem that a safe closure of the duodenum could be obtained by combining and simplifying these techniques. No doubt, as in all technical surgical problems solved under the stress of necessity, many surgeons have arrived at the same conclusion, but I have not discovered an account of the short procedure, and it may be of value to illustrate here the method of closure (*Fig.* 122). Although misgivings have been expressed about the unsoundness of closing the duodenum around the margins of a posterior ulcer, the method has so far proved reliable in 21 difficult operations.

The duodenum is divided obliquely so as to obtain a rather longer anterior than posterior duodenal wall, and the mid-point of the anterior wall is seized with a tenaculum forceps and held away from the posterior wall. The sides of the V so created are approximated with interrupted thread stitches until the duodenal orifice is narrowed, and the anterior part of the orifice (formed of duodenal wall) becomes about equal in length to the posterior part (bounded by pancreas) (*Figs.* 122, **a, b**). The 'pixie-cap' of anterior wall is now turned into the lumen and secured by a thread suture which takes a

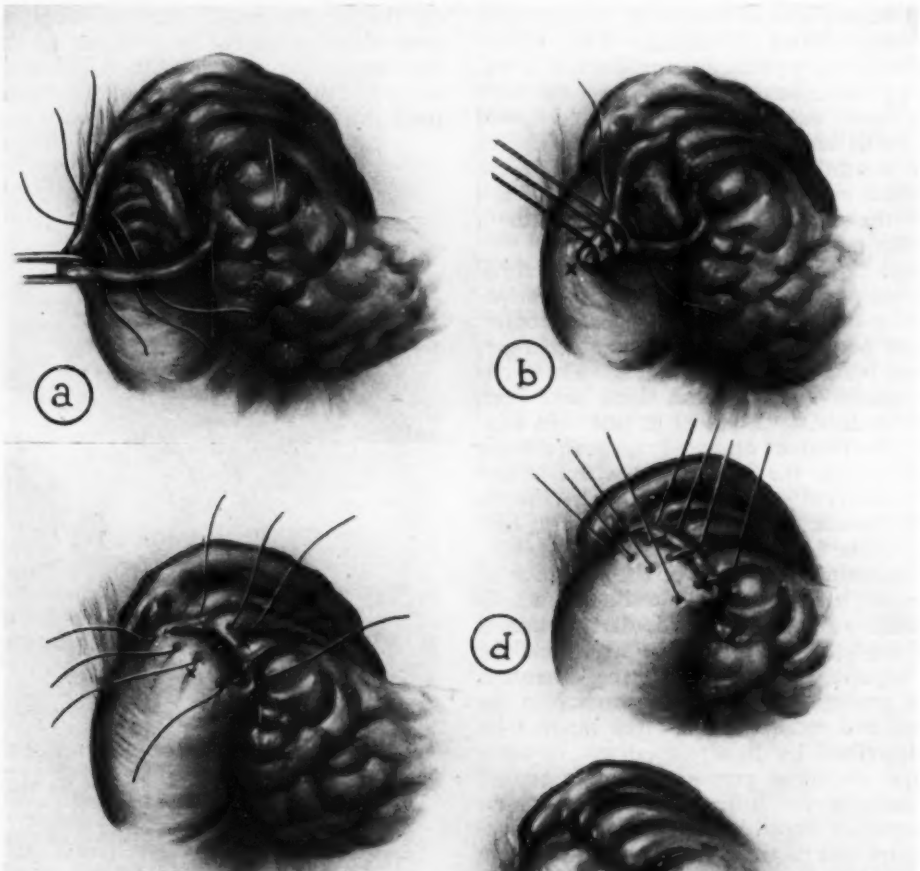


FIG. 122.—An inturning method of closure of the duodenum in the presence of a chronic penetrating ulcer in the posterior wall. **a, b,** The duodenal orifice is narrowed with interrupted thread stitches until the length of the posterior edge in the pancreas is about equal to that of the anterior part formed of duodenal wall. **c,** The 'pixie-cap' of anterior wall is now turned into the lumen and secured by a thread suture which takes a secure bite of the mid-point of the proximal rim of the crater in the pancreas behind and a seromuscular bite of the duodenal wall in front at the base of the 'cap' (X X). Similar sutures on either side of the central stitch complete this layer. In practice, the uppermost and lowermost sutures are passed first, to define and close these two danger points, and all sutures are passed and held 'long' before they are tied. **d, e,** A second layer of interrupted thread sutures is passed, each stitch taking a secure bite of the firm pancreatic rim behind, and a seromuscular bite of the duodenal wall in front.

firm bite of the mid-point of the proximal rim of the ulcer in the pancreas and a seromuscular bite of the anterior duodenal wall at the base of the 'cap'. A series of similar stitches on either side of this central stitch completes the first layer of sutures (*Fig.* 122, **c**). In practice, the uppermost and lowermost stitches are passed first, so as to be sure that the inferior and superior margins of the orifice are securely defined and closed; and all sutures are passed and held 'long' before any are tied.

A second layer of interrupted thread sutures is passed to bury the first layer, each stitch taking a secure bite of the thick edge or rim of the pancreas behind and a seromuscular bite of the anterior duodenal wall (*Fig.* 122, **d**). Local flaps of omentum are usually available to cover the suture line and so add extra assurance.

In this way the duodenum is closed without disturbing the ulcer or dissecting the posterior wall of the duodenum distal to the ulcer crater. In 21 operations in which this method has been used, 8 for uncontrolled bleeding from the ulcer base, and 13 operations of election for chronic posterior ulcer, healing has been obtained without leakage and with no subsequent ill effects. As these were all cases in which the hazard of gastrectomy is perhaps at its greatest, it has proved a welcome way out of an anxious problem.

The illustrations are the work of Mr. D. P. Hammersley, B.A., Medical Artist to the Department of Surgery in the University of Durham, to whom the author is much indebted for the precision and clarity of the drawing.

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SOME OBSERVATIONS ON THE FUNCTION OF THE SMALL INTESTINE AFTER GASTRECTOMY

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ONE of the functions of the stomach is that of a reservoir which stores food and prepares it for the small intestine, where the main processes of digestion and absorption are performed. The normal arrangement ensures that chyme enters the jejunum in an approximately isotonic state and at a suitable rate. After total gastrectomy and subtotal gastrectomy of the Polya type (in which the cardiac end of the stomach is anastomosed directly to the jejunum) food enters the small intestine almost at once without having been prepared by the stomach or duodenum, and its bulk or hypertonicity may give rise to a number of post-gastrectomy syndromes (Wells and Welbourn, 1951). We have been impressed by the *increased motor activity* of the intestine which may result, and have investigated the activity of the small intestine in relation to the 'efferent loop dumping syndrome' and to post-gastrectomy steatorrhœa. We have attempted to eliminate the factor of increased motor activity by giving various drugs, particularly C5 and C6 (penta- and hexamethonium bromide), which depress bowel movement.

1. **Effect of inflating Balloon in the Jejunum.**—Attempts were made to introduce a Miller-Abbott tube with balloon attached, into the efferent jejunal loop of 26 patients after gastrectomy (either Polya type or total). Preliminary anæsthetization with an amethocaine lozenge enabled the balloon to be swallowed without undue discomfort, and in 23 of the patients the balloon passed immediately into the jejunum, its position being checked radiologically (*Fig.* 123).

a. Symptoms.—With the patients recumbent the balloon was inflated with 20 ml. of air, with the following results:—

No. of Patients	*No. with Dumping Syndrome*	*Symptoms*
14	9	None
6	5	Sensation of epigastric fullness, nausea
3	3	Fullness, weakness in the legs, sweating, and nausea. They volunteered that these were the symptoms which they sometimes had after meals

Inflating the balloon with 30 ml. of air caused marked epigastric discomfort in all the patients, but did not produce dumping symptoms where these had not already been caused by inflation with 20 ml. of air. Inflation with 40 ml. to 60 ml. of air caused an aching pain.

b. Kymography.—Recordings of intestinal tone and contractions were made on a smoked drum by means of a tambour and lever system, which communicated with the rubber balloon of the Miller-Abbott tube. Varying patterns of intestinal activity were observed, and the two types of wave, described first by Ingelfinger and Abbott (1940), and later by Chapman and Palozzo (1949), were recognized. These are the long, low-frequency L

waves (of propulsion) and the short rapid non-propulsive S waves (of segmentation) (*Fig.* 124).

Inflating the balloon with 20 ml. of air produced a preliminary burst of activity (*Fig.* 125), especially pronounced in those subjects experiencing symptoms. This phase consisted of rapid frequency waves, similar to S waves except for their tendency to increase in amplitude as the symptoms became

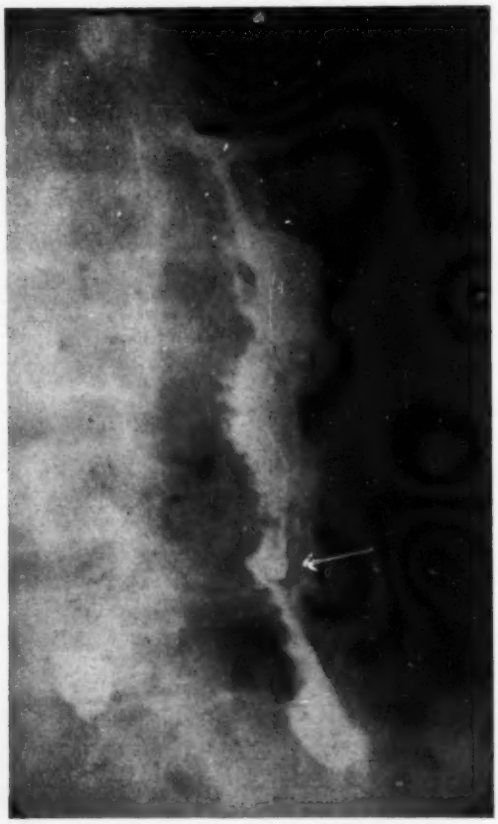

FIG. 123.—Radiograph showing tip of Miller-Abbott tube (arrow) in efferent jejunal loop after a Polya type of gastrectomy. A mouthful of barium has been given to outline the bowel.

worse. Their 'tonus level', however, tended to remain constant. Deflation of the balloon relieved the symptoms, and subsequent re-inflation produced 'normal' records for that patient (*Fig.* 125), the gut having become accustomed to the presence of the balloon.

2. Effect of introducing Hypertonic Solutions.—Hypertonic solutions were introduced into the jejunum in 9 subjects through the second 'suction' lumen of the standard Miller-Abbott tube. A number of apertures open into the bowel from this lumen, extending over 4 in. above and below the balloon, so that 20 ml. of fluid injected through this route do not exert as much distending force at any one point as 20 ml. of air injected into the balloon.

a. Symptoms.—In each of seven subjects a saturated solution of glucose produced 'dumping symptoms' (fullness, weakness, nausea, sweating, and palpitation) within five minutes of its injection. The amount required to produce symptoms varied from 5 ml. to 60 ml. The symptoms were relieved in two subjects within five minutes by the slow injection through the same route of 200 ml. of tap water at body temperature. In another subject 100 ml. of a saturated solution of protein hydrolysate ('Casydrol') was employed, and this produced the same symptoms as glucose. All the subjects were recumbent and the balloon was deflated.

For another subject (who had had a Polya gastrectomy with a small stoma) a Miller-Abbott tube was adapted so that the distal aperture was closed. Fluid could thus be introduced through the 'suction' lumen above the balloon but not below it. The balloon was then passed into the stoma and inflated with 60 ml. of air, so cutting off communication between the stomach and the efferent jejunal loop. 100 ml. of hypertonic glucose solution instilled through the 'suction' lumen into the stomach caused *no* symptoms with the patient recumbent or standing. Deflation of the balloon with the subject standing caused intense dumping symptoms within fifteen minutes. With the patient still standing 100 ml. of tap water were injected, and marked amelioration of symptoms resulted. A further 100 ml. of tap water caused the symptoms to disappear apart from slight residual nausea.

b. Kymography.—Inflation of the balloon with 20 ml. of air immediately before or after the instillation of concentrated solutions into the jejunum resulted in extreme nausea, retching, and vomiting of the balloon. The kymographic record was similar to that seen after the first air inflation of the balloon, except that the contractions were usually more violent (*Fig.* 124).

3. Effect of Methonium Salts on the Kymographic Record.—100 mg. of C5 or C6, injected intramuscularly or intravenously, caused loss of intestinal movement and tone (*Fig.* 126), the lever dropping and resting on the side of the tambour. This paralysis persisted for 20 minutes in the case of C5 given intravenously and for over two hours in the case of C6 given intramuscularly. Symptoms were relieved at the same time with the exception of nausea, which was inclined to persist. If C6 was injected before the instillation of 100 ml. of concentrated glucose solution into the jejunum, the symptoms of 'dumping' were prevented, again with the exception of slight nausea, and no excursions were recorded by the kymograph.

4. Effect of feeding a Meal of Barium and Hypertonic Glucose.—In order to obtain a visual record of the effect of hypertonic solutions on the small bowel a meal consisting of 170 g. of barium sulphate and 100 g. of glucose in 200 ml. of water was fed to 5 patients. In each case severe 'dumping' symptoms were produced, which came on within 5 to 15 minutes, and lasted for periods ranging from 20 minutes to 3 hours. The radiological appearances were as follows :—

R. P. (Polya gastrectomy, 'dumping syndrome', post-prandial diarrhœa, steatorrhœa).—Barium and glucose passed immediately into the pelvis, very active peristalsis was seen, and the head of the meal reached the hepatic flexure of the colon *in 5 minutes* (*Fig.* 127). Symptoms were present throughout. This was repeated, giving C6, 250 mg. by mouth 1 hour before the meal. There was much less activity, the symptoms were less, and

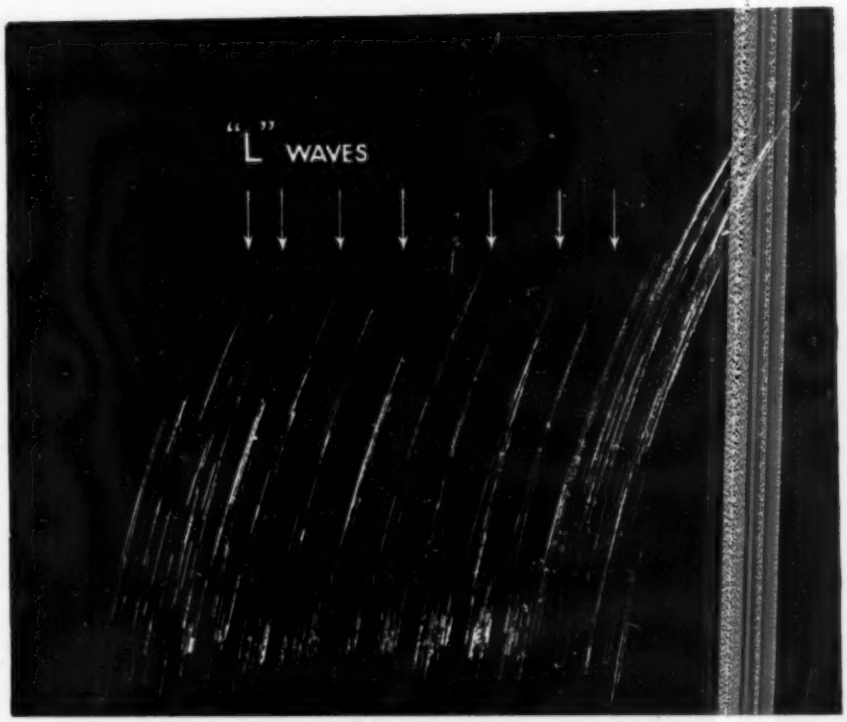

FIG. 124.—Kymographic record, showing L and S waves and effect of introducing hypertonic glucose into the jejunum. Male, aged 25, severe 'dumping syndrome' after subtotal gastrectomy.

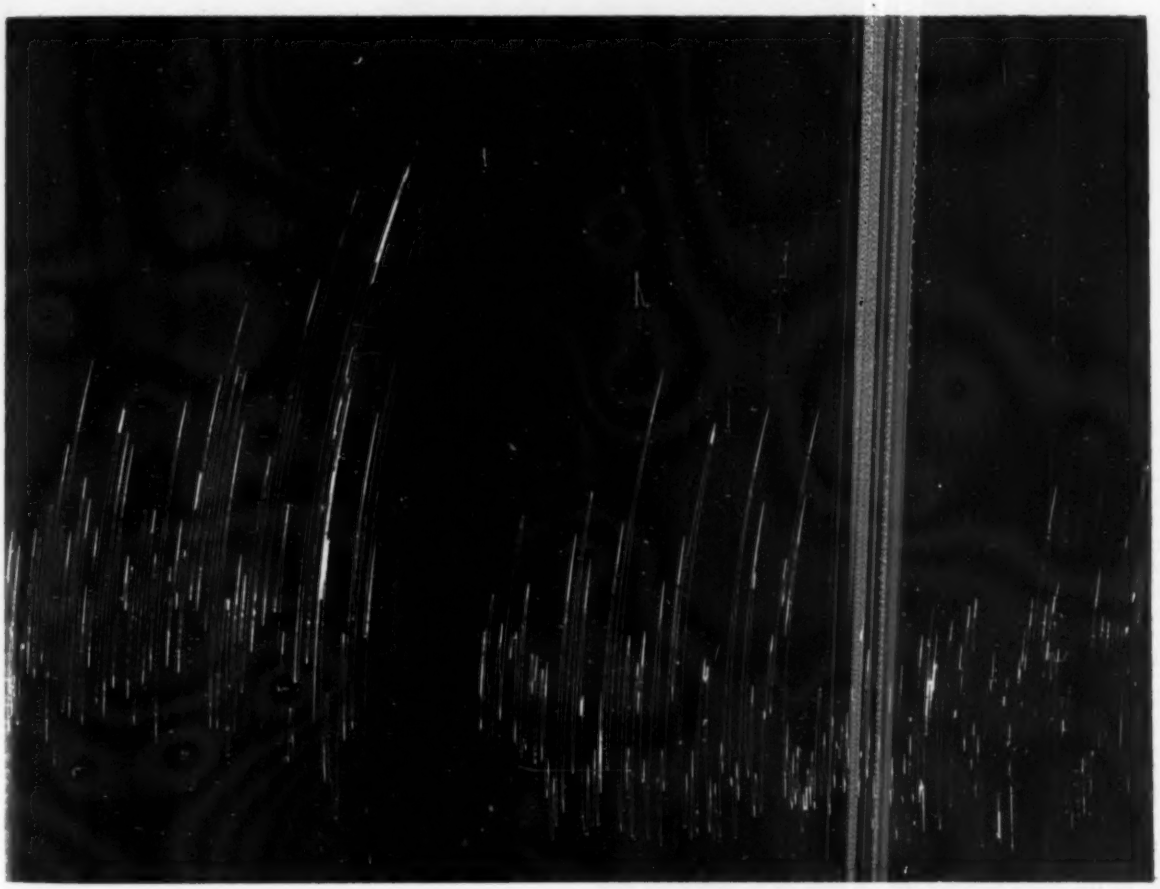

FIG. 125.—Kymographic record, showing effect of inflating balloon in jejunum, with 20 ml. of air. Male, aged 25, severe 'dumping syndrome' after subtotal gastrectomy.

the meal took 1¾ hours to reach the cæcum (*Fig.* 128). In this case segmentation of the barium is seen in the ileum, suggesting a 'deficiency pattern'. This appearance, however, is probably an effect of the hypertonic glucose.

J. C. (Polya gastrectomy, severe 'dumping syndrome').—An ordinary barium meal showed normal appearances, and was not accompanied by dumping of symptoms and activity. The bulk of the meal was still in the ileum after 2 hours.

G. G. (Polya gastrectomy, no post-gastrectomy symptoms).—Barium and glucose passed very quickly through the jejunum and had entered the ileum in 5 minutes. Thereafter activity became much less and the head of the meal had not entered the cæcum in 2½ hours. Severe 'dumping' symptoms were produced.

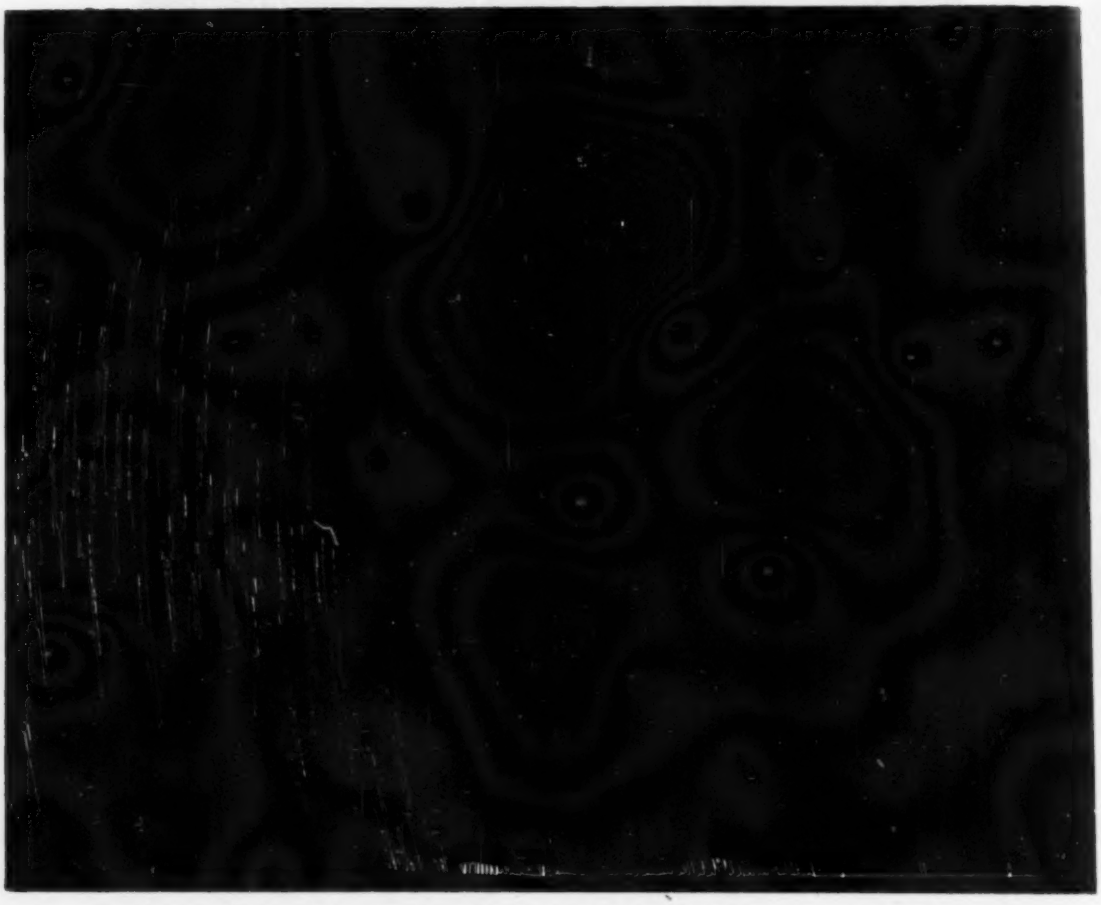

FIG. 126.—Kymographic record, showing effect of hexamethonium bromide (C6) on jejunal contractions and tone.

symptoms (*Fig.* 129 A). The head of the meal reached the cæcum in 3 hours. Within 5 minutes of swallowing a barium and glucose meal the jejunum became violently contracted, and the particles of barium were churned upwards and downwards at a great speed. Intense dumping symptoms, worse than usual, were experienced, and vomiting seemed imminent. In the time taken to place a loaded cassette in position and expose a film, the symptoms ameliorated slightly, and some relaxation occurred in the jejunum, although the appearances were still those of a very active bowel (*Fig.* 129 B); 50 mg. of C6 were then injected intramuscularly. All the dumping symptoms, except some residual nausea, passed within the next 2 minutes and at the same time the jejunum became inactive and was seen to dilate (*Fig.* 129 C). A film taken at one hour showed that the head of the meal had reached the cæcum.

W. D. (Polya gastrectomy, 'dumping syndrome').—Barium and glucose produced violent peristalsis, the head of the meal entered the cæcum in 17 minutes, and there were intense dumping symptoms. C6, 50 mg., was then injected intramuscularly with rapid diminution

H. T. E. (Total gastrectomy, mild dumping symptoms, steatorrhœa).—The findings were essentially the same as in G. G.

5. Post-gastrectomy Steatorrhœa.—It is well known that steatorrhœa may follow gastrectomy, but the mechanism by which it is produced is not clear. We thought it likely that the increased motor activity, which we had observed, might well play a part, and therefore tried to eliminate this factor by giving C6. The table on page 116 shows the results of 3-day fat-balance tests on 6 patients after gastrectomy (all of the Polya type, except H. T. E., who had had a total gastrectomy). The diet contained 50 g. of fat per day, which was divided between four meals. In each case the test was done first without C6, and then repeated, giving 250 mg. of C6 by mouth before the three main meals.

In the first two only was there marked steatorrhœa, and in these the absorption was increased by 11 per

cent and 15 per cent respectively when C6 was given. The C6 was continued for some weeks. R. P., who was 22 lb. below his health weight, put on 9 lb. in 6 weeks, and H. T. E., who was 36 lb. below weight, put on 20 lb. in 5 weeks. R. P. appeared to eat no more than before, but H. T. E.'s

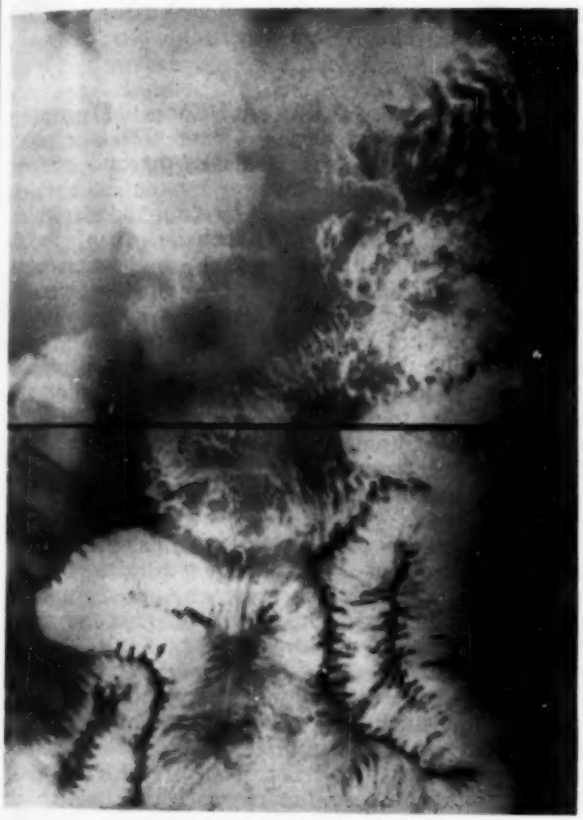

FIG. 127.—Radiograph taken 5 minutes after drinking a barium meal mixed with hypertonic glucose. The head of the meal has reached the hepatic flexure of the colon.

FIG. 128.—Same as *Fig.* 127, except that C6, 250 mg., was given by mouth 1 hour before the meal. A small quantity only of the meal has entered the small intestine.

A B C

FIG. 129.—Radiographs showing effect of barium and hypertonic glucose meal in another patient. C6, 50 mg., was injected intramuscularly 2 minutes before the third radiograph (C) was taken.

appetite increased. It is probable that the improved absorption of fat played some part in the weight increase. R. P. is the patient (described above) in whom the rate of passage of a hypertonic meal through the small intestine was greatly reduced by C6. The other 4 cases had fat absorption less than

Patient	Fat Balance Test					
	Without C6			*With C6*		
	Absorption	Split fat	Unsplit fat	Absorption	Split fat	Unsplit fat
	per cent	per cent	per cent	per cent	per cent	per cent
R. P.	76	74	26	87	73	27
H. T. E.	74	87	13	89	80	20
W. W.	92	44	56	91	75	25
G. G.	91	68	32	90	69	31
F. J. L.	87	54	46	88	94	6
E. J.	92	80	20	94	90	10

normal, but could not be said to have frank steatorrhœa. C6 had no significant effect on absorption, but in two (W. W. and F. J. L.) it appeared greatly to increase the proportion of split fat.

6. Clinical Effects of Methonium Salts.—The effect of C6 on 2 cases of steatorrhœa has already been described. Under experimental conditions C5 and C6 have greatly reduced ' dumping ' symptoms in most cases, but clinically, except in a few cases, they have proved disappointing in the relief of post-prandial symptoms. We used C5 at first, but later changed to C6 because it became available in tablet form (' Vegolysin ', May & Baker). In every case some other form of therapy or a placebo had been tried first. In the following cases these drugs were helpful :—

W. D. (Polya gastrectomy, ' dumping syndrome ').—C5, 250 mg. t.d.s. by mouth, before meals, caused a marked improvement in symptoms. C6 produced a still greater improvement, but headaches developed after a time, which the patient attributed to the C6. He now takes a dose before his main (evening) meal only, and eats a larger meal in comfort.

L. D. (Polya gastrectomy, severe ' dumping syndrome ').—C5, 500 mg. t.d.s. before meals, produced great improvement in all symptoms except post-prandial diarrhœa. (Since died from intercurrent disease.)

L. H. (Total gastrectomy, ' dumping syndrome ', steatorrhœa).—C6, 250 mg. t.d.s. before meals, reduced consciousness of intestinal movement, colic, and frequency of defæcation.

G. E. (Billroth I gastrectomy, sensation of fullness reduces size of meals).—C6, 500 mg. before the evening meal, enables him to eat much larger meal in comfort.

In the following cases C5 and C6 relieved ' dumping ' symptoms, but produced unpleasant side-effects :—

J. G. took 3 g. of C5 by mouth in 3 days and then developed blurring of vision, hunger, vasomotor collapse, and loss of consciousness. He responded to intramuscular ephedrine.

E. T. developed headache, aching in the eyes, and nightmares after taking C6, 250 mg., before his evening meal.

In 5 further patients C6 did not relieve ' dumping ' symptoms, and in one it appeared to aggravate them. In two it produced watery diarrhœa, and in one a papular rash (? bromide) developed on the arms. In one other case it relieved symptoms but a placebo was equally effective.

DISCUSSION

Mechanism of Efferent Loop ' Dumping Syndrome '.—The symptoms have been attributed to *distension of the jejunum* either by the bulk of food which enters it (Muir, 1949) or by the fluid which is poured out by the mucosa to dilute foods which form hypertonic solutions (Machella, 1949, 1950). We have confirmed Machella's observation that hypertonic solutions produce dumping symptoms, but have failed to reveal any dilatation of the jejunum while symptoms are present. Instead we have found an increase in motor activity with contraction and a tendency to spasm. This response of the small intestine to hypertonic solutions was demonstrated kymographically by Abbott, Karr, and Miller (1938), but they did not comment on the accompanying symptoms. It seems likely that it is the *increased motor activity* within the bowel that provides the adequate splanchnic stimulus for the production of ' dumping ' symptoms. And, provided the stimulus is great enough, symptoms may be produced in those who do not normally have a ' dumping syndrome ' (e.g., G. G. in (4) *above*). It is possible that hypertonic solutions cause an increase of motor activity, not by reason of the bulk which they attain after dilution in the bowel, but by the stimulation of special chemoreceptors. Very small quantities of hypertonic glucose rapidly cause greater activity than much larger quantities of isotonic glucose, and we have found that dilution of hypertonic glucose in the jejunum by 200 ml. of tap water has relieved symptoms (2*a*). On the other hand ' dumping ' symptoms often follow a meal which includes drinks, but can be avoided by taking dry meals. This point requires further investigation. An inflated balloon probably causes symptoms by stimulating activity. If it is inflated beyond a certain point pain, and not ' dumping ', results.

Butler and Capper (1951) believe that neural stimulation is caused by the traction on the œsophagogastric junction which follows operations of the Polya type or to stretching of the gastric remnant. Against this view are the facts that simple inflation of a balloon in the jejunum may reproduce the whole dumping syndrome, hypertonic glucose in the jejunum may cause symptoms when the subject is *lying down*, and hypertonic solutions may produce symptoms when introduced into the jejunum of a subject with an intact stomach (as in a feeding jejunostomy). In the experiment described in (2*a*) fluid in the stomach caused *no* symptoms, but marked ' dumping ' symptoms followed when it was allowed to drop into the jejunum.

Mechanism of Post-gastrectomy Steatorrhœa.—Emery (1935) has shown in the dog and Brain and Stammers (1951) have shown in man that if after gastrectomy fat is fed in small quantities a higher proportion of it is absorbed than if it is fed in larger amounts. This indicates that there is a

limit to the amount of fat with which the intestine can deal at any one time. Our results suggest that if the rate of passage through the small intestine is reduced, larger quantities of fat can be dealt with at one time. The fact that even with C6 our patients absorbed only about 90 per cent of their fat suggests that factors other than intestinal hurry may be involved. Lipolysis by bacteria, which interferes with particulate absorption of fat, may play a part (Frazer, 1949), and this may explain the observation of Emery (1935) that hydrochloric acid increased the absorption of fat in post-gastrectomy steatorrhœa.

Mode of Action of Methonium Salts.—Capper (1950) reported that T.E.A.B. (tetra-ethyl-ammonium bromide) would relieve 'dumping' symptoms, and Neligh, Holt, Lyons, Hoobler, and Moe (1949) showed that it depressed profoundly all motor activity in the stomach and small intestine. Methonium compounds are said to block all the autonomic ganglia (Paton, 1951), and it is probably for this reason that they depress intestinal activity. The relief of 'dumping' symptoms may be partly due to the depression of splanchnic stimuli and partly to the blocking of other ganglia involved in such reflex phenomena as palpitations and sweating. In some of our patients in whom relief was not obtained it was impossible to give a large enough dose because of the side-effects. Other cases, in which unexpected symptoms such as diarrhœa were produced, are hard to understand. Possibly the depression of sympathetic and parasympathetic elements is unequal, causing an imbalance.

SUMMARY

Observations are described on the relation of the small-intestinal motor activity to the efferent loop dumping syndrome and to post-gastrectomy steatorrhœa.

Inflation of a balloon in the efferent jejunal loop reproduced 'dumping' symptoms in 3 out of 23 patients. Kymography showed simultaneous increased motor activity.

Hypertonic solutions, introduced into the jejunum, caused 'dumping' symptoms constantly in 9 cases, and also produced marked activity on the kymograph.

The injection of methonium salts (C5 and C6) caused a diminution of dumping syndromes and profound reduction in jejunal activity and tone.

Hypertonic barium meals produced 'dumping' symptoms and marked activity in the jejunum in 5 cases. In one case a peristaltic rush caused the head of the meal to reach the hepatic flexure of the colon in five minutes. Methonium salts tended to reduce the activity seen radiologically.

In post-gastrectomy steatorrhœa C6 had no effect in 4 mild cases, but increased the absorption of fat in 2 cases of moderate severity, presumably by reducing the rate of passage through the small intestine.

Clinically methonium salts appeared to cause an increase in weight in 2 cases with moderate steatorrhœa. They relieved post-prandial symptoms in 4 cases. In 8 further cases they either had no beneficial effect or caused unpleasant side-effects.

The mechanism of the efferent loop 'dumping' syndrome is discussed, and it is concluded that *increased motor activity* in the jejunum provides the adequate stimulus for the production of symptoms.

This work was made possible by co-operation between the Ministry of Pensions and the Department of Surgery, the University of Liverpool. We wish to thank the Director-General of Medical Services, Ministry of Pensions, and Professor Charles Wells, of the University of Liverpool, for their ready assistance and their permission to publish the findings. We are also grateful to Messrs. May & Baker, Allen & Hanbury, and Burroughs Welcome for supplies of C5 and C6, and to Mr. W. Lee, of the Central Photographic Department, the University of Liverpool, for the photographs.

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GASTRECTOMY WITH REPLACEMENT*

A PRELIMINARY COMMUNICATION

By F. A. HENLEY

ASSISTANT SURGEON TO THE CENTRAL MIDDLESEX HOSPITAL; LATE SENIOR SURGICAL REGISTRAR, THE MIDDLESEX HOSPITAL

WITH AN INTRODUCTION

By RUPERT VAUGHAN HUDSON, London

There has been little fundamental change in the practice of gastric surgery since 1881 when Billroth performed his first partial gastrectomy for carcinoma of the stomach, and later devised the Billroth II operation which was subsequently to be modified by Polya 1911, and is popularly known by his name. There have been many alterations in technique in both these procedures, but the principle has been maintained, for the first is an end-to-end anastomosis between the stomach and the duodenum, whilst in the second the end of the stomach is implanted into a loop of jejunum.

Neither of these operations are without complications or disadvantages. The Billroth I operation enables food to pass through and be subjected to the action of the duodenum; the Billroth II excludes the duodenum from active contact with ingested food.

Moroney (1951) has published a series of successful cases in which he replaces the excised stomach with a detached portion of the transverse colon, and thus for the first time has there been a fundamental change in the technique and approach to gastrectomy.

While working in my Unit for the past five years, Mr. F. A. Henley has taken particular interest in the conduct of gastrectomy and the follow-up of gastrectomized patients. In many discussions together we were convinced that the Polya type of gastrectomy, although excellent in its relief of the symptoms for which it was performed, owed its primary fault to the exclusion of the duodenum, for in this operation food is no longer subjected to the contact and action of the duodenal mucosa. The duodenum, excepting its own idle secretions, becomes little more than an extension of the common bile and pancreatic ducts.

As a consequence, Henley, entirely on his own initiative, devised and performed the operation of jejunal replacement for the excised stomach. My own experience is limited as I have performed only three of these operations, with participation in a fourth. It is possible to affirm, however, that the immediate results have been very satisfactory.

The cause of gastric and duodenal ulcer is still unknown, and the Henley operation will necessitate prolonged trial and a follow-up extending over some years before it is known whether the threat of recurrent ulceration, which is always present in these patients, will subsequently take place in the gastric remnant or jejunal graft, or in the duodenum distal to the graft.

It is hoped by further study that the procedure will throw light upon the normal physiology of the stomach, duodenum, and digestive tract, and may further our knowledge of the causation of gastric and duodenal ulcer, for now it should be possible to obtain information as to the true effect the loss of the stomach has upon the individual, whereas formerly this study has been hampered by the gross physiological disorder produced by the Billroth II operation.

This is an interim report, as inevitably several years must elapse before any assessment of a new surgical procedure can be of real value.

Part of my work in the Wards and the Follow-up Clinic at the Middlesex Hospital dealt with patients who had had the majority of the stomach removed. For it was Mr. Vaughan Hudson's experience that the incidence of complications of gastric and duodenal ulcer increased according to the amount of the stomach remaining, and patients had been admitted with a recurrent ulcer in the form of the dreaded gastrocolic fistula as long as eighteen years after successful gastro-enterostomy, and some years after apparently successful gastrectomy. As a consequence, the operation of gastrectomy had been extended and the partial gastrectomy became subtotal (in the majority by the antecolic route), and approached the Visick (1948) measured gastrectomy.

It is agreed that this operation rendered the patients free from all their previous symptoms and recurrent ulcer so far has not been found. Radiologically, there was no filling of the afferent loop and the stomach emptied in half to one hour. The majority of patients did not gain weight, some had minor symptoms of which they made light, but one's impression was that these patients were not so well nourished as they should be, and it was felt that some would probably develop a deficiency state later in life.

The exceptional few had exchanged their previous ulcer syndrome for symptoms of the so-called post-gastrectomy syndrome, which limited their enjoyment of life and rendered them incapable of work demanding great activity. In-patient observation and laboratory tests upon these patients, and those from other Clinics, failed to reveal any specific change to differentiate them from those of their fellows who were free of these symptoms. One came to regard these patients, therefore, as suffering from a gross disorder of physiology due to the exclusion of the duodenum. It was felt that an attempt should be made to devise a procedure which would combine the virtues of subtotal gastrectomy and yet enable food to be subjected to the action of the duodenum.

* Accepted for publication March, 1952.

I determined therefore to devise a fundamental change in the technique of gastrectomy which would restore the continuity of the alimentary tract and be applicable to all lesions of the duodenum, stomach, and œsophagus, and to those cases of severe so-called post-gastrectomy syndrome consequent upon the Billroth II operation. It could be argued from the Billroth II operation that provided a subtotal gastrectomy was performed, the jejunum would withstand recurrent ulceration, and if this were so, it should theoretically also withstand recurrent ulceration if detached as a segment to replace the stomach.

My first case was that of a gastric ulcer and operated upon on August 13, 1951. Two further cases were completed before the operation was extended to other lesions. I have up to the present time performed this operation of jejunal replacement on 31 patients, and with the addition of Mr. Vaughan Hudson's 3 cases, and 1 combined case, the operation has been performed thirty-five times in all.

The operation has been used for the following :—

1. Total gastrectomy for carcinoma where the jejunal segment is anastomosed end-to-end between the œsophagus and duodenum. (2 cases.)
2. Subtotal gastrectomy for (*a*) removable gastric ulcer, and (*b*) removable juxtapyloric ulcer, where the jejunal segment is anastomosed to the cut end of the stomach and duodenum. (21 cases.)
3. Subtotal gastrectomy for (*a*) irremovable juxtapyloric ulcer, and (*b*) irremovable duodenal ulcer, where the ulcerated gut has been closed proximal to the ulcer and the jejunal segment anastomosed to the cut end of the stomach and to the side of the first or second part of the duodenum. (4 cases.)
4. Remedial replacement for the gastrectomy syndrome where the stoma has been left intact, the efferent limb sectioned a few inches below the stoma, and anastomosed to the side of the duodenum, and the afferent limb resected close to the stomach, its gastric end being closed, and the cut ends of the jejunum reunited. (4 cases.)
5. Jejunal replacement following subtotal gastrectomy for perforation of gastric ulcer (1 case), and duodenal ulcer (3 cases).

My first case was performed by the antecolic route. In the operation for remedial replacement where the previous Billroth II had been an antecolic operation, the mesentery of the replacement loop was permitted to remain in its original position. In all the remainder the retrocolic route was adopted.

In a new technical procedure modifications are bound to occur, and other surgeons who may wish to adopt the principle of the operation will modify the technique according to their own practice. One must stress, however, that this operation necessitates three separate anastomoses, and the safety of the operation depends particularly upon the blood-supply of the detached jejunal segment. The following are the details of the operation which I continue to perform at the present time.

DETAILS OF GASTRIC REPLACEMENT BY THE JEJUNAL SEGMENT

1. For Gastric Ulcer.—The abdomen is opened through a midline incision and, after section of the duodenum between Payr's clamps, the clamp on the duodenum is left in situ, the blades being gently swabbed with iodine and wiped dry with an unstitched dab.

The stomach is freed and held up at right angles to the abdominal outlet, and a special crushing clamp—as shown in *Fig.* 130—is applied, but before

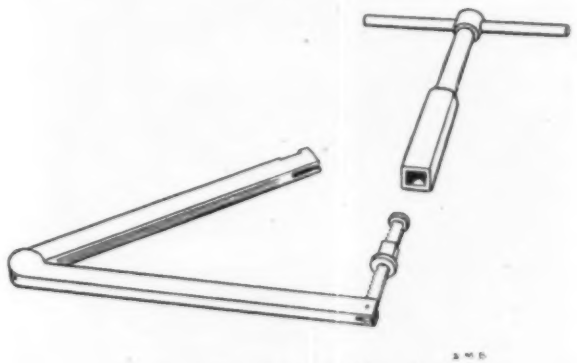

FIG. 130.—The gastric crushing clamp.

it is screwed tightly down the tension on the stomach is relaxed, so as to allow the stomach to slide back into the abdomen. By lifting the costal margin it is possible to see how much stomach is lying proximal to the clamp and at what angle the clamp is applied. Any necessary adjustment is then carried out and the clamp finally locked in order to procure its crushing effect. The redundant part of the stomach is left still in situ and lying turned upwards on the chest wall.

The transverse colon is now brought out of the abdomen and the duodenojejunal junction of the small intestine is identified and the jejunum immediately distal to this point is turned upwards piece by piece until the jejunal segment will remain in the intended position without any tension on the mesentery. The segment of jejunum selected will vary between 4 and 8 in. in length according to the amount of stomach and duodenum removed. The blood-supply to this segment of jejunum is next examined, both for its arterial supply and for an adequate venous drainage, and when the site has been chosen, the V-shaped mesentery is separated from the remainder of the jejunal mesentery. It is usually necessary to ligate at least one vascular arcade in this manœuvre. The requisite segment of jejunum is then isolated between de Martel clamps, and the isolated segment is gently turned upwards and covered on both its surfaces with a warm, wet swab, while the cut ends of the jejunum and its mesentery are anastomosed in continuity.

For this purpose, interrupted No. 2 silk sutures —usually about four or five in number—are placed between the two cut ends of the jejunum, the de Martel clamps are then removed, and these sutures are tied to appose the posterior seromuscular layers. A continuous or interrupted atraumatic catgut suture

is next applied to all layers until the lumen is reconstituted, and finally the second layer of seromuscular sutures is applied anteriorly, again of No. 2 silk. The gap in the mesentery is likewise closed

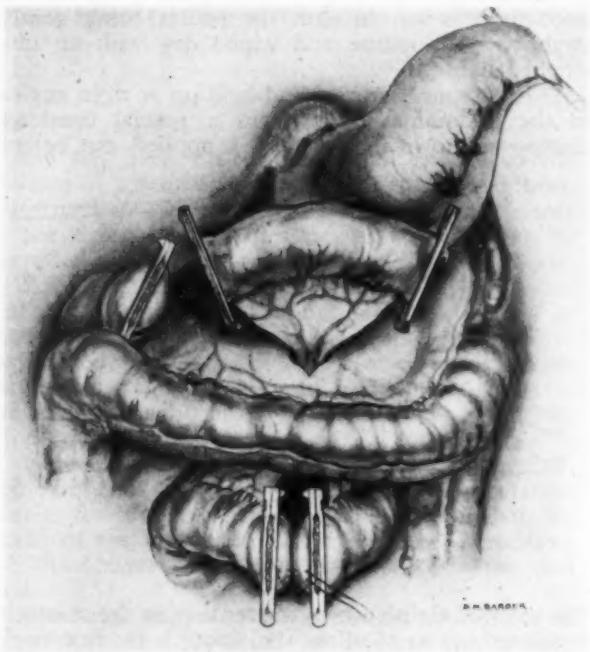

FIG. 131.—Showing isolated segment of jejunum taken retrocolically into upper abdomen.

in apposition with No. 2 silk, usually two or three being necessary, and great care being taken not to penetrate any blood-vessels in this mesentery.

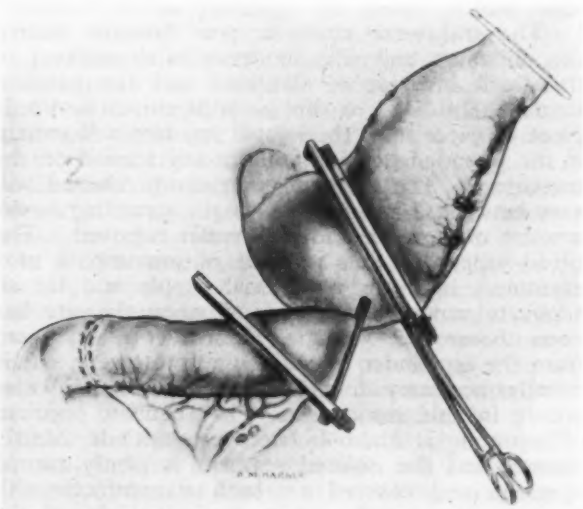

FIG. 132.—The jejunoduodenal anastomosis being completed and the crushing clamp is in position on the proximal end of the jejunal graft.

The jejunum is now replaced in the abdomen, the transverse colon is held in the hands of the assistant and the surgeon like a frame, and an avascular area will always be seen close to the posterior abdominal wall and to the left of the middle colic artery. This is incised from left to right and then elongated anteriorly to make a foramen of about 2 in. diameter. The isolated jejunal segment with its small de Martel clamps applied is now passed through this foramen into the upper abdominal cavity (*Fig.* 131), great care being taken to mark the proximal end of the segment from the distal (for this purpose I apply an Allis tissue forceps to the proximal end and only remove it whilst it is going through the transverse mesocolon and immediately re-apply it).

Interrupted No. 2 silk sutures are now applied between the seromuscular coat of the duodenum and that of the distal end of the jejunum. The clamps are then removed from the duodenum and the distal end of the jejunum as the sutures are tied to approximate these two structures. An interrupted atraumatic suture is next applied through all layers of the jejunum and duodenum and the

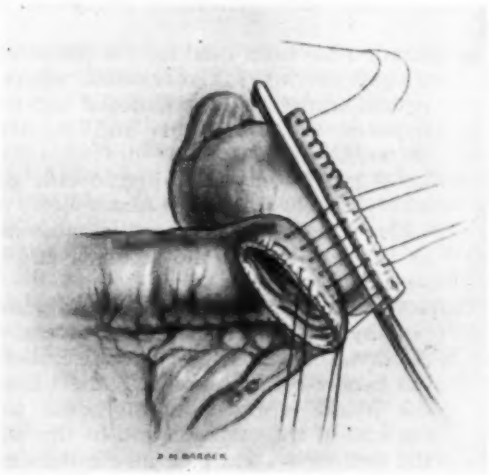

FIG. 133.—Demonstrating Stage 1 of the gastrojejunal anastomosis.

anterior surface is finally completed, again with interrupted No. 2 silk sutures (*Fig.* 132).

A holding clamp is next placed on the gastric remnant. The stomach is aspirated and lifted out of the abdominal cavity, and, whilst the assistant holds the clamp, the redundant portion of the stomach is removed and the blades of the crushing clamp swabbed in iodine and wiped dry with an unstitched dab. A continuous silk stitch is now placed through half the gastric stoma just beneath the crushing clamp, beginning at the lesser curvature end. The crushing clamp is then removed, and a pair of Taylor's tissue forceps is placed on the greater curvature of the stomach at the stomal angle. The crushing clamp is now applied to the jejunal segment (*Figs.* 132, 133) and the segment is cut obliquely in order to enlarge the stoma (*Fig.* 133). Interrupted silk sutures are again applied between the stomal edge of the stomach through its seromuscular layers only and those of the proximal end of the jejunal segment, the clamp is then removed from the latter, and the sutures are tied to approximate these two structures. Starting in the middle of the posterior wall, a continuous atraumatic suture is applied round to the anterior surface and completed

by a second atraumatic suture working in the opposite direction until the lumen is closed (*Fig.* 134).

The anterior layer of interrupted silk sutures is now applied between the stomach and the proximal end of the jejunum, the lesser curve half of the

FIG. 134.—Stage II of the gastrojejunal anastomosis.

gastric stoma is now invaginated, using interrupted seromuscular sutures, and a special interrupted stitch is applied between the jejunum and the lesser curvature of the gastric remnant. The operation is completed by closing the hiatus in the transverse

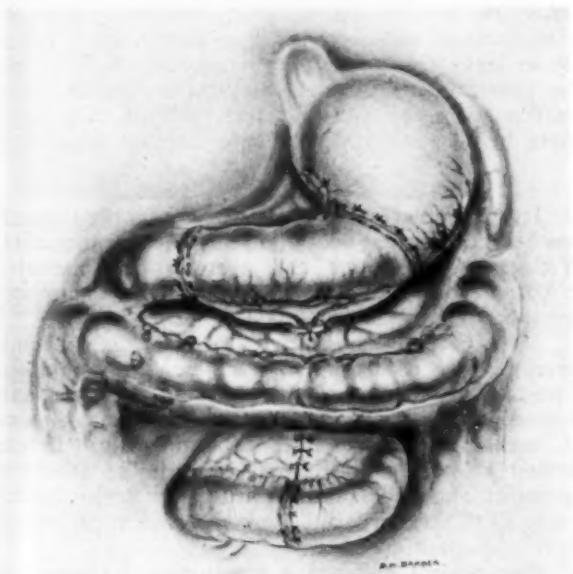

FIG. 135.—The final disposition of the jejunal graft between the stomach remnant and duodenum, and showing also the jejunal anastomosis.

mesocolon with one stitch, which also picks up a small bite of the mesentery of the isolated segment to prevent any mobility at this site. *Fig.* 135 shows the final arrangement.

Five grams of microcrystalline sulphathiazole powder are then dusted on the three anastomotic lines and the abdomen is closed in layers without drainage.

2. For Duodenal Ulcer.—The technique is precisely the same as that described above, differing only at the duodenal anastomosis. If the ulcer is a duodenal ulcer which is removable, or a juxtapyloric ulcer, part of the first part of the duodenum

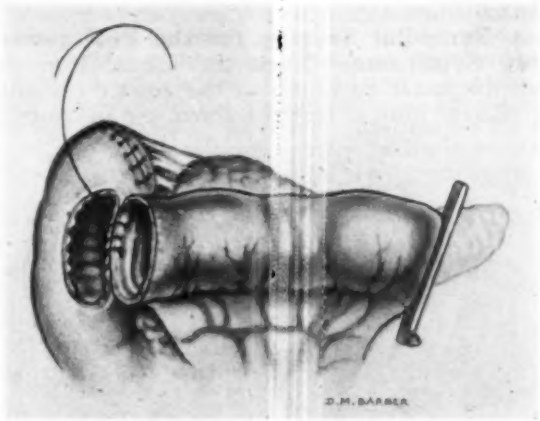

FIG. 136.—The end-to-side anastomosis between jejunum and duodenum.

is removed with the stomach and the distal end of the jejunal segment is anastomosed end-to-end to the second part of the duodenum.

For an irremovable duodenal or juxtapyloric ulcer, the end of the duodenum or pylorus is oversewn in one or two layers and the distal end of the jejunal segment is anastomosed to the side of the second part of the duodenum on its anterolateral aspect (*Fig.* 136). This is achieved by precisely the same technique, using interrupted seromuscular silk sutures and only removing the clamp of the

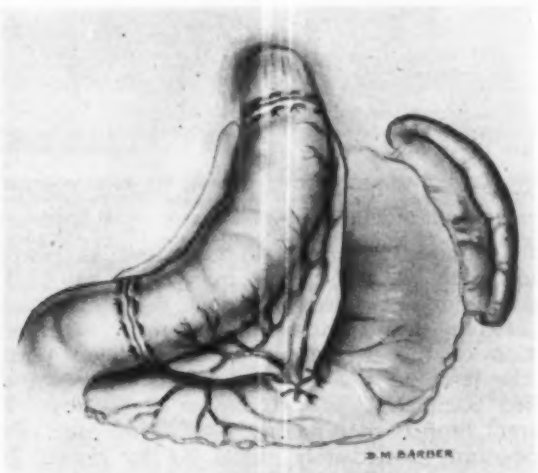

FIG. 137.—The final stage of total gastrectomy with the jejunal segment between the œsophagus and the duodenum.

jejunum on knotting the sutures and drawing them together. The atraumatic sutures are then applied through all layers, and finally the anterior seromuscular silk sutures are applied.

3. For Total Gastrectomy.—The technique of jejunal replacement of the stomach is precisely as above, but the whole stomach is removed and the

œsophagus and proximal part of the jejunal segment are approximated end-to-end, using two layers of sutures as in all other anastomoses. The segment of jejunum in a total gastrectomy will be at least 8 in. in length and at the completion of the operation will lie slack in diastole and take on the attitude of the stomach (*Figs.* 137, 138).

4. Remedial Surgery for the Post-gastrectomy Syndrome.—When the jejunal loop runs from the lesser curvature to the greater curvature, the efferent limb is resected about 5–6 in. from the

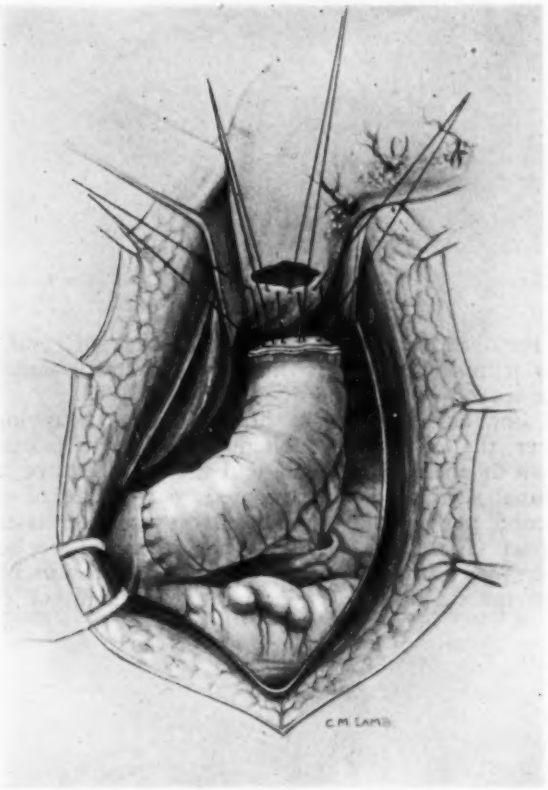

FIG. 138.—Total gastrectomy. Showing the œsophagojejunal anastomosis in progress.

stomal outlet and the afferent limb is resected immediately at the stomal inlet (*Fig.* 139). The free afferent and efferent limbs are then anastomosed to restore the jejunum in continuity, and after section of the mesentery to the isolated portion of the jejunum the afferent bud is oversewn and closed completely by two layers of sutures. The efferent limb is then anastomosed to the side of the duodenum immediately distal to its closed end. If the previous Polya type operation has been one where the afferent loop goes from the greater curvature to the lesser, then the operation is simplified, as the efferent limb will already be travelling in the right peristaltic direction, and a shorter jejunal segment will be required to anastomose it to the duodenum (*Fig.* 140).

TYPES OF OPERATION

1. Retrocolic.—The retrocolic operation appears to give the easiest access technically, and would appear to be both anatomically and physiologically the correct procedure. At the end of the operation the contents of the abdomen lie without tension. There are no loops or bands of mesentery, and no possible hernial orifices for gut to enter.

2. Antecolic.—The antecolic operation has been performed once only, and that in my first case. This route was abandoned for the retrocolic method at Mr. Vaughan Hudson's suggestion.

The antecolic is in danger of two possible complications: (*a*) the irritative action upon the transverse colon by the mesentery of the jejunal segment, and the possibility of changes occurring in this mesentery with impairment of the vascularity and mobility of the jejunal segment; (*b*) a loop of small gut may find its way above the transverse colon and behind the detached mesentery of the jejunal graft, giving rise to chronic, and later acute, intestinal obstruction. This complication has been personally seen a year after a Billroth II operation. It is particularly interesting to record that my first case of jejunal replacement suffered this complication four months after this operation. This patient had to be re-operated upon for a reduction of the internal hernia, albeit with a successful outcome.

3. Remedial.—In the remedial operation following the Billroth II operation, the previous route may have been the antecolic or the retrocolic. In the retrocolic type the remedial operation is straightforward. In the antecolic there are three alternatives: (*a*) to break down the anastomosis and take the whole segment behind the colon and re-anastomose it to the stomach; (*b*) to divide the transverse colon and its mesentery and re-anastomose it in front of the detached jejunal mesentery; and (*c*) to leave the antecolic jejunal loop in situ. At the present time this last method is considered to be the less hazardous and less difficult in spite of there being some risk of future internal herniation.

DISCUSSION

Jejunal replacement of part or the whole stomach has been performed on 35 patients without mortality. With two exceptions the average post-operative in-patient stay has been fourteen days. Complications occurred in 6 patients.

Two patients submitted to total gastrectomy developed a leak at the œsophagojejunal anastomosis. The first was a minor perforation on the eighteenth post-operative day due to swallowing a tough piece of steak. This leak healed spontaneously. In the second a leak occurred forty-eight hours after the operation and necessitated re-suture. Both patients made a full recovery, but the complication prolonged their in-patient stay.

One patient suffered a reactionary hæmorrhage at the gastrojejunal anastomosis and was re-operated upon twenty-four hours later, with a successful outcome.

Of the remainder, 2 developed a left pulmonary collapse which responded quickly to treatment; and 2 other patients a post-operative thrombosis of the posterior tibial vein—treatment with anticoagulant therapy was successful and their in-patient stay was not delayed.

It is fair to state that all cases of chronic gastric or duodenal ulcer were patients with long histories

and many of them had been complicated by previous attacks of hæmatemesis or melæna. In the normal course the majority would have been submitted to a Billroth II operation; in a few instances it might have been possible to perform a Billroth I operation.

Economy of space forbids a full report on all patients, but the following are typical case-histories illustrating the lesion, the operation, and the follow-up results.

For Carcinoma of the Stomach.—

M. H., female, aged 52. Housewife. This patient was admitted under the care of Dr. F. Avery Jones on Oct. 20, 1951. She had been investigated as an out-patient, and a barium-meal examination showed the proximal two-thirds of the stomach replaced by neoplastic tissue. She was submitted to total gastrectomy and jejunal replacement on Oct. 29, 1951.

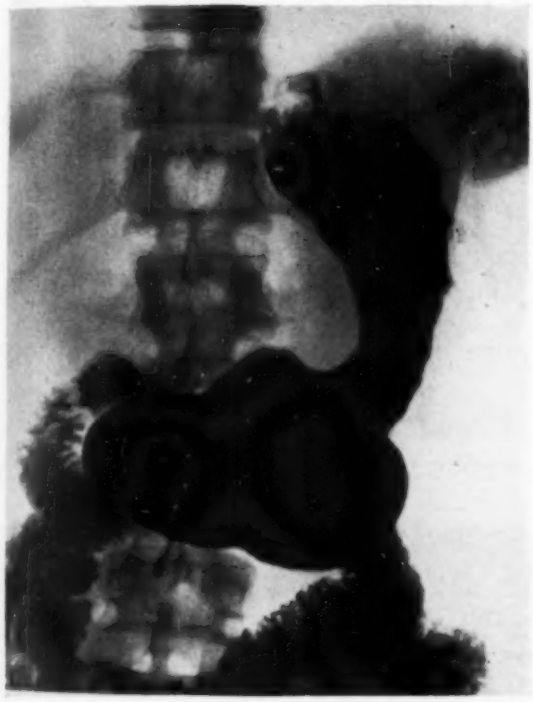

FIG. 139.—M. H., showing carcinoma of the stomach.

POST-OPERATIVE COURSE.—This was eventful on two accounts. The intravenous drip which contained Casidrol, 10 per cent glucose, an ampoule of Becosym, and 30 c.c. of alcohol in a litre of saline, given by means of a polythene tubing, leaked through the axillary vein and flooded the subcutaneous tissue of the right abdominal wall, causing intense pain. This was quickly remedied by the local injection of hyaluronidase. Henceforth she made a normal recovery, but on Nov. 19, whilst eating steak, she suddenly experienced acute retrosternal pain with simultaneous pain in the left shoulder and around the left lower ribs. Feeding by mouth was stopped, a Ryle's tube passed into the stomach and she was given chloramphenicol. A small barium meal showed a fistulous subphrenic abscess in communication with the lower œsophagus. It was decided to treat the patient conservatively, and after five days the Ryle's tube was removed and fluid intake recommenced by mouth. A further series of radiographs showed the subphrenic abscess to be decreasing in size, and the last taken on Dec. 12 showed the subphrenic abscess to be completely healed, by which time the patient was on full diet and asymptomatic. She was discharged home on Dec. 15.

PATHOLOGICAL REPORT.—Specimen: Total gastrectomy with left and right gastric and right gastro-epiploic vessels.

The whole of the body and fundus of the stomach are replaced by a nodular thickening of their walls with ulceration of the mucosa. The peritoneal coat of the stomach wall is involved, especially on the posterior aspect of the body of the stomach, but there is nowhere any actual ulceration through the peritoneal coat. In addition there is infiltration of the greater omentum at scattered points along the greater curvature. The mucous membrane of the pyloric antrum appears relatively normal.

FIG. 140.—Same case. Post-operative appearance, showing œsophagojejunal anastomosis end-to-end and jejunoduodenal junction end-to-end.

Histology.—Section shows invasion by poorly differentiated adenocarcinoma of high-grade malignancy.

Spread: (1) Local—invasion of omental fat along greater curvature—peritoneal involvement but not actual ulceration. (2) Lymphatic—of 14 glands sectioned, 11 showed involvement by tumour, including glands at the point of ligature of the left gastric artery. (3) Blood-borne—not seen.

Classification: C_2; high grade of malignancy; Stage III. *Figs.* 139 and 140 illustrate the pre- and post-operative appearances.

FOLLOW-UP.—When seen on Jan. 30, 1952, she had a good appetite, ate a normal diet, and enjoyed her food. Whereas formerly her complexion was pallid, she is now healthy in colour and of a cheerful disposition. Her pre-operative weight was 6 st. 10 lb. and on this occasion was only 6 st. 7 lb. When seen again, on March 24, she had no indigestion, flatulence, or pain after food, and when questioned about her energy said she was "full of fight". Her weight was 7 st. 4 lb., and she had therefore gained 10 lb. since her last visit, and is 8 lb. more than her pre-operative weight. With a very small barium meal the jejunal segment now shows an increase in tone and empties in half an hour.

For Removable Gastric Ulcer.—

J. D., male, aged 46. Storekeeper. Admitted under the care of Dr. Avery Jones on Aug. 14, 1951, with a gastric ulcer on the posterior wall just above the angulus. He gave a history of dyspepsia since 1934, with a relapse in the spring and autumn of 1937, and at this time radiology showed a gastric ulcer. He had a similar relapse in 1939 and periodically since then. He had been off work for many months in the past and for the five weeks prior to admission. His highest known weight was 16 st., and his present weight 11 st. 8 lb. Operation Aug. 27, 1951.

FIG. 141.—J. D., showing gastric ulcer and size of stomach.

POST-OPERATIVE COURSE.—Uneventful. Was taking a full diet on Sept. 6, and was discharged on Sept. 8.

HISTOLOGICAL SECTION confirmed the presence of a chronic gastric ulcer with no evidence of malignancy.

FOLLOW-UP.—When seen on Oct. 17, his weight was 12 st. 13 lb. and he had therefore gained 1 st. 5 lb. in six weeks. He admits to being ravenously hungry and can eat without discomfort.

Fig. 141 shows clearly the large gastric ulcer, and *Fig.* 142, taken on Nov. 3, shows the barium meal passing through the jejunal segment. The gastric remnant was completely empty in two hours.

For Removable Duodenal Ulcer and Gastric Ulcer.—

H. N., male, aged 58. Printer's reader. A chronic gastric and duodenal ulcer. This patient was admitted under the care of Dr. Avery Jones on Dec. 3, 1951, with a recurrent history of both a gastric and a duodenal ulcer since 1947. In Nov., 1949, a gastric and duodenal ulcer were found by the radiologist, and on admission both these ulcers were again proved to be present. Examination showed him to be emaciated and in severe pain, of which he complained unceasingly. His weight was 8 st. 5 lb. Operation Dec. 6, 1951. Both these ulcers were penetrating the pancreas, and both were dissected free, the gastric ulcer leaving a cavity in the pancreas approximately a half-inch in diameter. This was oversewn.

POST-OPERATIVE COURSE.—Uneventful. The patient was discharged on Dec. 21, 1951, and the histological section proved both these ulcers to be benign.

FOLLOW-UP.—When seen on Feb. 2, 1952, his weight was 8 st. 7 lb., a gain of 2 lb. only, but he had lost all his symptoms and felt " quite a different man ". He was eating well and taking full meals without discrimination, and there were no post-prandial symptoms.

FIG. 142.—Same case. Post-operative appearance showing small gastric remnant and end-to-end jejunoduodenal anastomosis.

For Removable Duodenal Ulcer.—

L. R., male, aged 64. Retired. Chronic duodenal ulcer. Admitted under the care of Dr. Avery Jones on Oct. 12, 1951, as an emergency ; he had been vomiting for twenty-four hours. His dyspepsia dated from 1938. Hæmatemesis in 1939 and a proven duodenal ulcer. 1942 : recurrence of symptoms. November, 1950 : hæmatemesis. January, 1951 : melæna and recurrence of pain. Barium meal again demonstrated a duodenal ulcer. In view of this long history it was decided to submit him to surgery, and he was operated upon on Nov. 5.

POST-OPERATIVE COURSE.—Uneventful. The patient was discharged from hospital on Nov. 17.

Figs. 143, 144 show the pre- and post-operative appearances of the gastro-intestinal tract as demonstrated by barium-meal examination. The emptying time was two hours.

HISTOLOGICAL REPORT.—Chronic duodenal ulcer.

FOLLOW-UP.—On Oct. 14, 1951, his weight was 9 st. 8 lb., and when seen on Dec. 29 his weight was 10 st. 11 lb., a gain of 17 lb. He had no symptoms and requested permission to find light employment. On direct questioning he felt well, eats small meals, but can eat anything. He has no bowel dysfunction and his energy is good.

For Irremovable Duodenal Ulcer.—

J. R., male, aged 49. Electrician. Chronic duodenal ulcer. Admitted under the care of Dr. Avery Jones on

Oct. 29, 1951. A history of indigestion periodically for twenty years. In 1941 a peptic ulcer was diagnosed, and in 1950 a barium meal showed a duodenal ulcer.

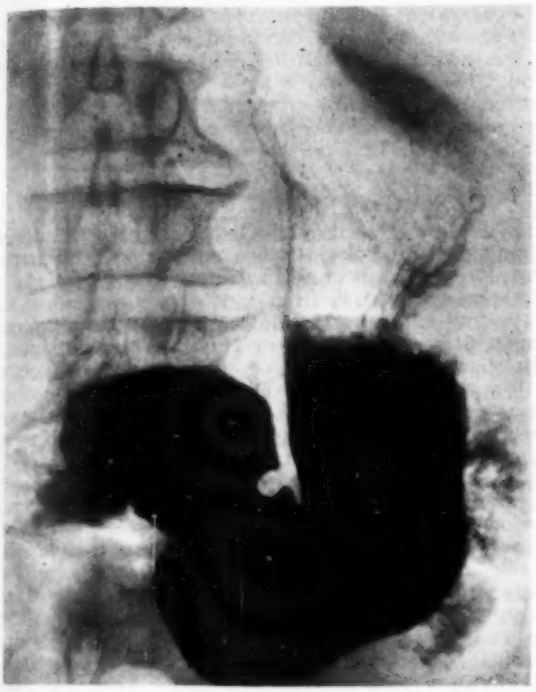

FIG. 143.—L. R., fixed duodenal ulcer with pyloric stenosis.

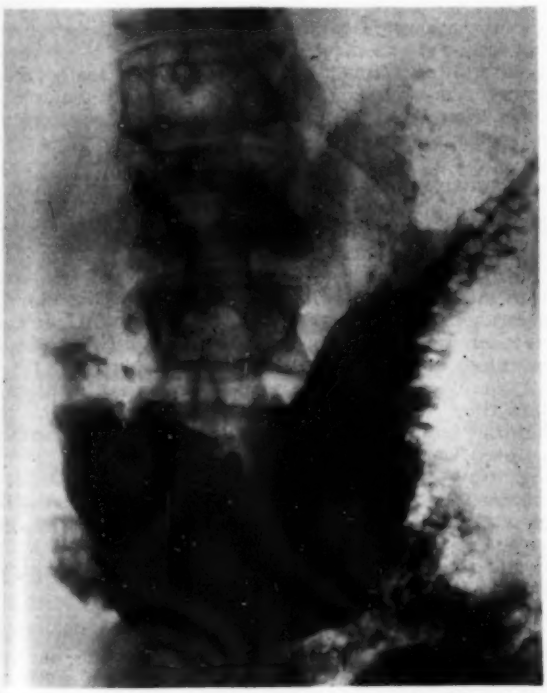

FIG. 145.—J. R. Pre-operative appearance of duodenal ulcer.

He vomited on occasions, and suffered small hæmatemeses in October, 1950, and again in May and August, 1951. His epigastric pain had been continuous since March, 1951, and from that time he had done little work. Operation Nov. 5, 1951. The pyloric end was oversewn and the distal end of the isolated jejunal segment was anastomosed to the side of the second part of duodenum.

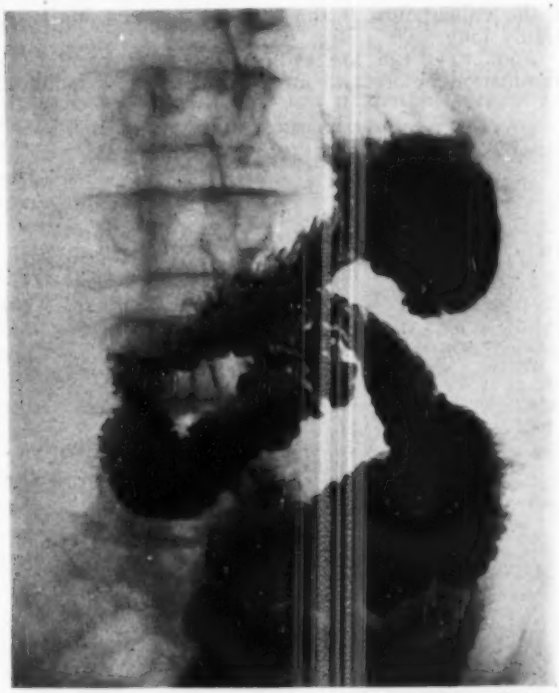

FIG. 144.—L. R. Post-operatively showing residual small gastric remnant and jejunoduodenal anastomosis end-to-side.

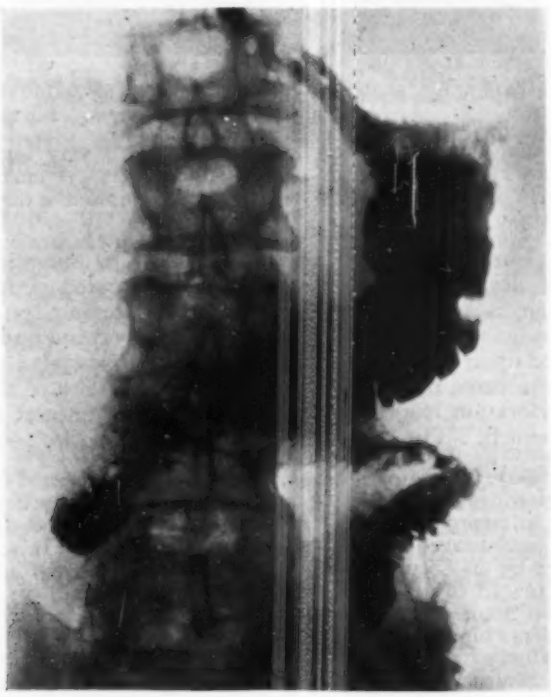

FIG. 146.—Same case. Post-operative barium meal showing jejunal graft between gastric remnant and duodenum.

POST-OPERATIVE COURSE.—On Nov. 14 he developed a deep thrombosis of his left calf and was therefore placed on anticoagulant therapy; the remainder of his convalescence was uneventful and he was discharged on Nov. 23.

FOLLOW-UP.—His weight was 9 st. 12 lb. at operation, and when seen on Jan. 7, 1952, his weight was 10 st. 10 lb., a gain of 12 lb. He was quite well in himself on this occasion, but mentioned that he had slight discomfort in the epigastrium if the interval between meals was unduly long.

Figs. 145, 146 are radiographs of a barium-meal examination before and after surgery. The radiologist

FIG. 147.—G. J. C. Six weeks after gastrectomy and jejunal replacement following perforation of a duodenal ulcer.

reports that the gastrojejunal appearance is very satisfactory and emptied in two hours, whereas pre-operatively only three-quarters of his stomach emptied in three hours.

For Perforated Peptic Ulcer.—The operation has been performed in 4 cases of perforated peptic ulcer, in 1 case of gastric ulcer, and the remainder in duodenal ulcers. All patients were received and operated upon within eight hours of their perforation; in these cases it was possible to remove the site of the perforation, together with the necessary amount of stomach. The following is an illustrative case :—

G. J. C., male, aged 50. Weighbridge clerk. Perforated gastric ulcer. Admitted into one of my beds as an emergency with a history that at 5 a.m. that day he was awakened with severe epigastric pain. He was seen by his doctor at 7 a.m., who gave him a sedative and requested to be called again if the pain became worse. Two hours later he was again seen by his doctor, who ordered him to hospital as the diagnosis was now apparent. His only history was of one year's epigastric discomfort after meals, with occasional vomiting, and a barium-meal examination performed elsewhere three months earlier had revealed no ulcer. Operation Nov. 22, 1951, seven hours after perforation. A large perforation 1 cm. in diameter was found high up on the lesser curvature.

POST-OPERATIVE COURSE.—He developed a productive cough, an exacerbation of a persistent cough which he had had since an attack of pneumonia seven years earlier. He made a full recovery and was discharged from hospital on a normal diet on Dec. 8, 1951.

FOLLOW-UP.—When seen in the Follow-up Clinic on Feb. 20, 1952, his condition was very satisfactory, he was taking a normal diet, and his appetite was very good. His weight was 8 st. 8 lb. The barium meal showed a more rapidly emptying stomach than is usual, the gastric remnant and jejunal segment being empty in one hour (*Fig.* 147).

For Post-gastrectomy Syndrome.—

S. T., male, aged 46. Owner of glazier business. Complained of persistent bile vomiting since his gastrectomy for gastric ulcer. His history was as follows: a hæmatemesis in 1938 from a proven gastric ulcer. In 1945 admitted to the Middlesex Hospital with perforated gastric ulcer just above the angulus. This was sutured; post-operatively he developed a lung abscess which was dealt with by thoracotomy and drainage. He developed severe symptoms owing to the recurrence of his gastric ulcer, and in September, 1947, a partial gastrectomy was performed of the antecolic Polya type, from which he made an uneventful convalescence. Nine days after operation he complained of slight indigestion, and when seen in the Follow-up Clinic two months later he complained of loss of weight, anorexia, and repeated vomiting of bile. A barium-meal examination showed a good gastric stump which emptied only into the efferent limb, the stomach being completely empty in one hour. There was no rapid emptying, no jejunal dumping, and no jejunitis. A month later these three symptoms persisted and he began to show marked wasting. When questioned closely he said he often vomited between one and two hours after a meal, and nearly always after lunch and breakfast. The vomit consisted purely of bile, no solid food ever being present. He further had a marked distaste for butter, margarine, and other fats. He believed that lying supine after a meal lessened the chance of his vomiting, and on regaining the erect posture nausea returned. Further full investigation by Mr. Vaughan Hudson as an in-patient failed to reveal an organic lesion to account for these symptoms. Between this time and November, 1951, he was repeatedly examined and given a variety of treatments. There was no marked improvement beyond a slight gain in weight of 2½ lb. He then started again to lose weight, and he was advised and gladly accepted further surgery.

On Nov. 18, 1951, he was admitted to the Middlesex Hospital under the care of Mr. R. Vaughan Hudson (his weight then being 8 st. 13 lb.) and on Nov. 20 the remedial operation was performed, from which he made an uneventful convalescence.

FOLLOW-UP.—When seen *en route* for a Convalescent Home three and a half weeks after the operation, his bile vomiting had not returned, and the only comment expressed was by his wife, who was pleased that he was going away " as he was eating her out of house and home ". When seen on March 13, 1952, his weight was 10 st. 11 lb., a gain of nearly 2 st. He expressed himself well satisfied with the result, and was able to eat normal food, including fats and sugars. The barium meal showed an emptying time of just over two hours.

A. B., female, aged 48. Housewife. Post-gastrectomy bile vomiting. This patient was admitted under the care of Dr. Avery Jones on Dec. 1, 1951, with the following history: She had a duodenal ulcer with symptoms on and off for twenty years, and on Jan. 23, 1951, a partial gastrectomy was performed. Two weeks after operation she began bile vomiting. After leaving hospital she had an attack of diarrhœa, which persisted for two weeks. Her stools were very watery in consistency, were passed hourly by day and by night, and occasionally contained

blood and mucus, and she complained of troublesome tenesmus. Central abdominal colicky pain was associated with the diarrhœa and relieved by defæcation. When diarrhœa ceased, vomiting became her only symptom. She vomited every day about noon-time and occasionally in the evening, and this vomiting had no definite relationship to meals. The vomit was green, frothy, and did not contain food or blood; the act was preceded by intra-abdominal gurgling lasting a few minutes. She felt quite well immediately after vomiting. Her weight was 6 st. in August, 1951. In an endeavour to correct the bile vomiting, the surgeon re-operated upon her on Aug. 2. He found nothing abnormal and re-made the gastrojejunal anastomosis. She remained well for one month, after which vomiting re-commenced, and was identical with that following the first operation. She was also getting attacks of colicky pain which were radiating from the epigastrium through to the back and along the left iliac crest. This discomfort was relieved by eating, vomiting, rest, and the application of local heat. She had now become constipated. Examination revealed no abnormality. Her blood-count showed a degree of iron deficiency. On Dec. 10, 1951, she was submitted to the remedial operation, and it was found that at her previous operation the anastomosis was an antecolic Polya type with the afferent limb passing to the greater curvature of the stomach.

POST-OPERATIVE COURSE.—Uneventful. She was put on full diet seven days after operation, developed a good appetite, and was discharged home on Dec. 22.

FOLLOW-UP.—When seen three months after operation her weight was 8 st., which is a gain of 2 st. Her appetite was very good and there was no post-prandial discomfort and no bowel dysfunction. She had vomited on five occasions soon after returning home, but not since; at times she is conscious of a gurgling sensation in the left subcostal area. She expressed herself well satisfied with the operation. A barium meal performed March 31, 1952, showed the gastric remnant to be completely empty in two hours, and no delay at the site of the jejunal anastomosis.

THE FOLLOW-UP

Of the 35 patients submitted to jejunal replacement and discharge from hospital between Aug. 13, 1951, and March 1, 1952, 8 treated after Jan. 1, 1952, are too recent for discussion. It may, however, be stated that their immediate results have been very satisfactory.

The remaining 27 patients have been followed-up for not less than three months, and although this time is very short, it is possible to give a general summary of their present state.

General Condition.—This has been satisfactory in all cases. The patients feel well, their energy is good, and they are free from lassitude and post-prandial dyspepsia.

Weight Increase.—Where there has been no post-operative complication, patients have usually regained their pre-operative weight within six weeks of the operation. The maximum weight gained has been just under 2 st., and the minimum 2 lb.; the majority have put on a stone in weight. The exceptions are two cases of carcinoma of the stomach, both of which had an eventful convalescence.

Appetite.—The majority of patients affirm that their appetite is very good, they are ready for food, enjoy it, and eat a normal diet. They tend to limit the amount of food eaten at each meal, and this is in accordance with the small gastric remnant.

Alimentary Function.—There has been no instance of bile vomiting, dumping syndrome, or large bowel dysfunction, the bowel habit of the patient having returned to that which was normal for him prior to the onset of his disease. Particularly gratifying have been the immediate results of the remedial operation for the so-called post-gastrectomy syndrome: the poor appetite has given way to a normal desire for food, and the distaste for fats and sugars has disappeared; the persistent weight loss has been steadily regained.

The Radiographic Appearance.—The average post-operative appearance three months after the operation of subtotal gastrectomy demonstrates the anatomical continuity of the gastro-intestinal tract.

Under the screen barium enters the gastric remnant and appears to be "milked" by the peristaltic action of the jejunal graft into the duodenum. The average emptying time of the stomach and graft is two hours. So far neither the gastric stump nor the jejunal graft have undergone dilatation, and the jejunal graft has maintained its normal tone.

The length of the jejunal segment varies from case to case, and the impression gained is that the longer the segment the slower the emptying time, and the shorter the segment the more active its peristalsis.

CONCLUSIONS

The immediate results suggest that the plea for the preservation of the duodenum as an active component in digestion has been borne out.

These results also strongly suggest that the lack of increase in weight, the anæmia, and the so-called post-gastrectomy syndrome following the Billroth II operation are due to the exclusion of the duodenum.

By employing a segment of jejunum as a method of performing a Billroth I operation subsequent to partial gastrectomy, food is held in the gastric remnant and delivered slowly by jejunal peristalsis into the duodenum, so that the emptying time of the gastric remnant and graft approaches more closely to that of the normal stomach. In the Billroth I operation food may enter the duodenum hurriedly, with subsequent dilatation and a degree of ileus of the duodenum. In the presence of a jejunal graft food is delivered to the duodenum slowly and more in accordance with the normal physiology of the upper alimentary tract.

SUMMARY

A preliminary report is given of the operation of replacement of part or the whole of the stomach by a segment of jejunum. This operation has been performed 35 times without mortality from Aug. 13, 1951, to March 1, 1952. Complications have been 6 in all, 2 necessitating further surgery, but the remaining 4 responded to medical treatment.

The technique of the operation has been fully described.

In order to explore the extent of the operation it has been performed for a variety of lesions: carcinoma of the stomach 2; gastric ulcer 13; removable duodenal ulcer 8; irremovable duodenal ulcer 4; perforation of peptic ulcer 4; remedial for post-gastrectomy syndrome 4.

The immediate results have been encouraging, and the average in-patient stay, with two exceptions, fourteen days.

A brief review of 27 patients followed-up for three months or longer is given. The general condition and appetite has improved. The maximum weight gained has been 26 lb., the minimum 2 lb., and the average 14 lb. There has been no so-called post-gastrectomy syndrome or bowel dysfunction. The average emptying time of the stomach and graft depends upon the length of the jejunal segment; in the majority this is two hours.

Particularly gratifying have been the immediate results of the remedial operation for the so-called post-gastrectomy syndrome.

It is emphasized that a long follow-up is necessary prior to a final assessment of the value of the operation. So far the immediate results justify the claim that the preservation of the normal physiology of the duodenum plays an important part in the post-gastrectomy result.

Typical case notes are included. The technique of the operation is illustrated, and post-operative radiographic studies are presented.

It has been my privilege to have had the guidance of Mr. Vaughan Hudson in the preparation of this paper. I am indebted to him for his suggestions, stimulating encouragement, and support when the idea of this operation was discussed with him, and for permission to include his cases.

To Dr. F. Avery Jones and Dr. Richard Doll I am indebted for their kindness in entrusting the cases to my care.

For the barium-meal examinations and their reports, and permission to reproduce the radiographs, I wish to thank Dr. F. Pygott and Dr. M. G. Scott, of the Central Middlesex Hospital, and Dr. C. G. Whiteside, of the Middlesex Hospital.

I should also like to thank Dr. W. Pagel, of the Central Middlesex Hospital, Professor Robert Scarff, and Dr. B. Morson, of the Bland-Sutton Institute of Pathology of the Middlesex Hospital, for the pathological reports.

I wish also to place on record the help given to me by my assistants, Messrs. J. W. Jackson, T. P. S. Watts, and William Slack.

The excellent drawings are the work of Miss D. M. Barber, and the clear photography that of Mr. A. G. Booker.

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THORACIC INLET NEUROVASCULAR INTERFERENCE

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THE title of this article has been deliberately selected so as to include the various clinical conditions produced by pressure on, or displacement of, the brachial plexus and subclavian artery in the region of the thoracic inlet, thus producing a syndrome similar to that usually ascribed to the presence of a cervical rib.

BRIEF HISTORICAL SURVEY

Cervical ribs have been known from the time of Galen, and recognized as a source of irritation to the adjacent structures since Hunault's paper in 1714, but it was not until 1861 that Coote removed the extra rib with marked relief of the patient's symptoms. This encouraged further investigation of the condition, particularly into the development and anatomy of these ribs and to the factors producing the symptoms. At the Royal Society of Medicine in 1913, Wood Jones formulated the idea of pre- and post-fixed plexuses, and suggested that the vascular symptoms were due to sympathetic nerve irritation and not to direct pressure on the subclavian artery. Sargent (1913) stated that it was more common for the fibrous end of the rib to cause pressure, and Buzzard (1913) noted the multiple types of upper arm pain and the importance of work as a precipitating factor. These theories all laid emphasis on the angulation of the plexus and artery over the cervical rib as a cause of the symptoms.

Although as far back as 1905 Murphy had called attention to the importance of the scalenus anticus in compressing the plexus and artery against the cervical rib, it was not till 1927 that Adson and Coffey suggested that division of this muscle was the sole procedure necessary to relieve the pressure. This was undoubtedly a great therapeutic advance, for all the previous literature had testified to the morbidity following operative removal of a cervical rib. Arising from this, it was soon realized that the scalenus anticus could be the major source of compression against a normal rib. In fact, these two authors had mentioned " A group of anomalies in the supraclavicular triangle which give rise to symptoms similar to those of cervical rib ".

In 1935, Ochsner, Gage, and De Bakey published a comprehensive study on this theme, outlining a ' Scalenus Anticus Syndrome ', giving a great deal of the credit to their colleague, Naffziger. Since then much has been written developing this theme, and other anomalies in the thoracic inlet causing similar symptoms and signs have been described.

AETIOLOGY

It has been a long-established fact that cervical ribs only produce symptoms in a small percentage of the subjects in whom they occur. To explain this Wood Jones (1911, 1913) suggested that there is normally a developmental ' antagonism ' between the ribs and the brachial plexus, so that if the ribs come higher up the vertebral column, i.e., there is a cervical rib, the brachial plexus also tends to take origin from the higher nerve-roots—' prefixed plexus ' ; whilst, if the ribs tend to be placed lower on the vertebral column, the reverse holds good, viz., the plexus is ' post-fixed '. Where this antagonism does not occur, a cervical rib, or even a normal first thoracic rib, can cause pressure on the plexus.

Todd (1912) also postulated a developmental defect, but clinicians generally favour some acquired factor as an exciting cause of the symptoms, which seldom appear until well on in life, even if a cervical rib is present.

Buzzard (1913) originally suggested that this acquired factor was a dropping of the shoulder-girdle resulting from undue work, e.g., carrying, muscular weakness, etc. Adson and Coffey (1927) thought more specifically that in the young, over-development of the scalenus anticus was caused by excessive work and exercise, whilst in older people there was muscular weakness with a resultant drop in the shoulder-girdle, causing tightness of the scalenus anticus, so that this muscle would press on the brachial plexus or subclavian artery. This naturally applies whether a cervical rib is present or not.

Gage (Ochsner, Gage, and De Bakey, 1935) and others hold that there is a vicious circle of definite spasm of the scalenus anticus—possibly initiated by trauma—which irritates the brachial plexus, including the supply to the scalenus anticus which maintains the spasm. To explain the continued irritation of the nerve-supply of the scalenus anticus (cervical 4 and 5), Swank and Simeone (1944) suggested that the spasm of the muscle gripped the cervical *nerve-roots* in a vice composed of the slips of origin of the scalenus anticus in front, and the transverse processes of the cervical vertebræ, a cervical rib, or a scalenus medius behind. Despite the many anatomical studies which have been made to demonstrate this idea, it still remains only a possibility.

An entirely different view, put forward by Eden (1939) and Falconer and Weddell (1943), attributes symptoms to the nipping of the nerves and artery between the clavicle and either the 1st rib or a bulbous end of a cervical rib, when the shoulders are braced back. Several observers (Eden, 1939 ; Walshe, Jackson, and Wyburn-Mason, 1944) testify to this mechanism compressing the artery, but few make definite reference to nervous irritation. A more recently described mechanism is that of hyper-abduction of the arm, whereby the neurovascular bundle is kinked under the coracoid process and pectoralis minor (Wright, 1945 ; Paull, 1946). This is, however, a fairly normal occurrence, and symptoms are unlikely to appear unless a person has his arm hyper-abducted for many hours at a time as Todd showed on himself in 1922.

While there is no doubt that the pain and muscular wasting is due to pressure on the neural structures, the aetiology of the vascular symptoms is hotly disputed by two opposing schools of thought.

1. That the vascular lesions are due to direct pressure on the subclavian artery, either by the cervical rib as originally described, or by the scalenus anticus (Adson and Coffey, 1927 ; Smith, 1940 ; MacFee, 1940), or by nipping between the clavicle and the rib (Eden, 1939 ; Falconer and Weddell, 1943 ; Walshe and others, 1944). Intermittent occlusion of the artery is held to explain the transitory attacks of ischæmia, whilst damage to the arterial wall following prolonged and repeated trauma could lead to thrombosis, embolism, or aneurysmal dilatation. Much thought and effort have gone to explain (Falconer and Weddell, 1943 ; Halsted, 1916 ; Reid, 1916) why this latter occurrence is usually distal to the cervical rib.

2. The symptoms are due to irritation of the sympathetic nerves as they run in the brachial plexus. Stopford and Telford (1919) showed that on some occasions at least they run as a separate nerve in the lower part of the brachial plexus and are thus very liable to compression. By this theory, the ischæmic attacks are vasospastic phenomena, and the local damage to the subclavian artery is due to the spasm of the vasa vasorum, with resultant degeneration of the arterial wall (Telford and Mottershead, 1947).

CLINICAL PICTURE

As previous observers have often emphasized, the clinical picture is essentially the same whatever the precipitating factor (Walshe and others, 1944 ; Craig and Knepper, 1937 ; Naffziger and Grant, 1938 ; Aynesworth, 1940 ; Donald and Morton, 1940 ; Patterson, 1940).

The patient is more frequently a female and usually between 40 and 50 years of age.

Nervous manifestations include pain in the shoulder-girdle, usually over the deltoid, the side of the neck, or between the spine and the scapula. This tends to be of an aching character and occasionally extends around the chest wall. In addition, the patient complains of shooting pains down the forearm to the fingers, and sometimes *up* from the fingers to the forearm and shoulder. This lancinating pain may be of ulnar or radial distribution or may be described as being ' down the centre '. The fingers affected vary greatly and are not necessarily of comparable distribution to the forearm pain. Some cases have no forearm pain, though the symptoms are marked in the fingers. Paræsthesiæ are a major complaint, usually associated with the pain and affecting the same area of distribution : when closely questioned, some patients have meant paræsthesiæ when they have complained of pain. A frequent comment is that ' pins and needles ' pass up the arm on tapping the fingers. Nearly all patients complain of numbness of the fingers, sometimes all five, but usually only the ones in which they have pain. Objective demonstration of diminished sensation, though not infrequent, is less commonly found.

Coldness, usually limited to the painful fingers but occasionally affecting the whole hand, is often a marked symptom.

Weakness of the grip and of the whole arm is a common symptom which appears to be due partly to the poor co-ordination, and partly to the true muscular weakness which is apparent in clinical tests. Muscular wasting is seen, usually in the small muscles of the hand, but sometimes in the forearm. The groupings most often found are the two types described by Wilson (1913)—' median ', with selective wasting of the abductor pollicis brevis and opponens pollicis ; and ' main en griffe ', with wasting of the hypothenar and interossei muscles.

The vascular effects most often noted are coldness and pallor, though a persistent dull red colour or the occurrence of Raynaud-like phenomena occasionally occur. More definite manifestations of vascular compression are diminution or obliteration observed in the radial pulse with such manœuvres as depression of the shoulder, turning the head away from the affected side, or to the affected side, with a deep inspiration (Adson's test), abduction of the arm, etc. Many observers have queried the pathogenicity of these ' tests ', and shown that the same effects can be brought about in normal subjects (Wright, 1945 ; Telford and Mottershead, 1947 ; Theis, 1939).

The subclavian artery may be damaged at the site of compression resulting in a local thrombosis and, on some occasions, ischæmia and gangrene of the digits (Eden, 1939 ; Walshe and others, 1944 ; Smith, 1940 ; Hill, 1939). These may be due to emboli, as it is doubtful if simple occlusion of the subclavian artery would cause such marked effects. Sometimes the subclavian artery is rendered unduly prominent in the supraclavicular triangle, leading to the complaint of a pulsating tumour there, but, very rarely, it may be truly aneurysmal (Murphy, 1905 ; Eden, 1939 ; MacFee, 1940). This feature is not limited to those cases in which a cervical rib is present (Shumacker, 1946). Digital pressure in the supraclavicular region may cause the typical pain of which the patient complains and is a useful sign.

It is of great interest that the symptoms are often precipitated by certain acts, particularly carrying and abduction. In many cases, the history will reveal that a few months before the onset of symptoms the patient has altered her occupation to one in which this particular action is more pronounced, or has increased laborious household duties.

DIFFERENTIAL DIAGNOSIS

This must be carefully considered in all cases and includes : Progressive muscular atrophy ; syringomyelia ; ulnar neuritis ; arthritic pains, particularly of the cervical spine ; pressure on the spinal cord or brachial plexus due to other causes such as neoplasms ; Raynaud's disease ; ruptured intervertebral disk ; supraspinatus cuff inflammation ; and subacromial bursitis.

PRESENT SURVEY

Our studies in this field have been conducted by the careful clinical observation of patients in the wards and out-patient department. Thirty have been submitted to operation, but this report is based particularly on 20 consecutive cases admitted for operation between November, 1948, and September, 1950, whom we have been able to follow up for a minimum of six months.

Abstract of Clinical Features.—

Sex.—There were 11 females and 9 males.

Age.—13 were between 40 and 52 years ; 6 were between 16 and 32 years ; 1 was aged 60. The average age, 41 years.

History.—This varied between one month and five years, though one case complained of vague pain for twenty years.

Side of Lesion.—Left side, 10—minimal symptoms on right as well in 4 ; right side, 7—none with symptoms on left ; bilateral, 3. (None of these patients were ' left-handed '.)

Site of Pain and Site of Paræsthesiæ.—

Back of neck	9 (45 per cent)	None
Deltoid	14 (70 per cent)	None
Inner side of brachium	3 (15 per cent)	None
Whole forearm	0	5 (25 per cent)
Ulnar side of forearm	7 (35 per cent)	5 (25 per cent)
Radial side of forearm	1 (5 per cent)	1 (5 per cent)
Fingers	5 (25 per cent)	12 (60 per cent)

Numbness.—This was complained of in some degree by 18 patients (90 per cent).

Change of Colour.—10 patients (50 per cent) complained of colour changes, of which 7 patients complained of whiteness during the attack, 2 with Raynaud-like phenomena ; 3 patients complained of blueness during the attack.

Weakness.—This was complained of by 6 (30 per cent) of patients, whilst wasting and coldness were each the complaint of one patient.

Factors precipitating an Attack.—11 patients (55 per cent) noted this—3 by any work ; 3 by lifting and carrying—the weight of his clothes was sufficient for one man! ; 1 by washing clothes ; 1 by turning the head ; 3 by flexion and abduction of the arm (i.e., working in a low coal seam, working at an artist's easel, holding up a cooking pot).

Change of Work.—9 patients (45 per cent) had altered their occupation to something heavier a variable time before the onset of symptoms. Apart from this, no specific occupation seemed particularly to cause symptoms.

Wasting.—This was observed in 10 patients (50 per cent) and was distributed as follows: thenar eminence 7 ; hypothenar eminence 7 ; interossei 6 ; forearm muscles 2.

It is of interest that 4 patients with total history times of 6, 5, 3, and 1 month respectively showed very definite wasting.

Power.—This was objectively diminished in 8 patients. Four showed general weakness of the arm ; 3 had a poor grip ; 1 had weakness of his intrinsic muscles only.

The Radial Pulse.—This was affected by posture in 7 patients (35 per cent).

a. Adson's test caused obliteration of the radial pulse in 3, marked diminution of the radial pulse in 2.

b. Abduction of the arm caused obliteration of the radial pulse in 3.

Minor degrees of change and the effects of traction on the arm were disregarded in view of the established unreliability of these manœuvres (Wright, 1945 ; Telford and Mottershead, 1947 ; Theis, 1939).

A disconcerting fact discovered late on in the series was that these effects on the pulse were not constant in the same patients.

Temperature.—The temperature of the affected hand was found to be markedly reduced in 9 patients. In no case was it raised, even though the hand sometimes looked a dull red.

Colour.—The colour of the affected hand was observed to be changed in 7 patients (35 per cent). In 4 it was paler than the other, in 2 it was redder than the other, and in 1 it was bluer than the other. In only 3 of these patients, one with a red hand and two with blue hands, was the pulse affected by posture.

Sensation.—In 6 patients this was dulled—all in the ulnar distribution.

Supraclavicular Space.—1 patient without a bony cervical rib had an obvious swelling here, whilst palpation caused typical pain or paræsthesia in 3 patients.

X-ray Findings.—2 cases had distinct bony cervical ribs, 1 cm. long; 2 cases had long transverse processes to the 7th cervical vertebra. These patients showed no significant difference in clinical picture.

TREATMENT

This series does not reflect a complete view of the disease, particularly in respect of therapy, for these 20 cases were all ones in whom symptoms were regarded as sufficiently severe to warrant operation.

Two other groups were seen at Out-patients :—

1. Those with such mild symptoms that they cleared spontaneously with rest. The usual procedure was the wearing of a sling for a week or a fortnight, followed by the avoidance of heavy lifting for a further month.

2. Those with symptoms that cleared with adequate physiotherapy directed at increase of shoulder muscle tone. As a general rule, however, recovery was not quite 100 per cent.

In this present series, 7 patients had failed to benefit by, or had relapsed badly after, a prolonged course of physiotherapy.

Operative Procedure.—This was similar in all cases. The posterior triangle of the neck was explored through an incision above the inner one-half of the clavicle. The clavicular head of the sternomastoid was then divided and the fatty connective tissue gently separated to disclose first, the posterior belly of omohyoid which was divided, and then the scalenus anticus. At this point, with all the relevant structures in view, but undisturbed, a careful visual and digital examination was made to try and discover the site of distortion or strain. Particular note was taken of: (1) Scalenus anticus —its tightness and any obvious part it was playing in compression or distortion of the artery or plexus. (2) The first rib. (3) Whether there was anything deep to the plexus materially holding it forward.

The scalenus anticus is divided by carefully cutting on to a dissector with a knife. This "slow-motion cross-sectioning" of the muscle showed a very interesting variation in its structure; in particular, the deep part was commonly tendinous with a distinct and sometimes sharp lateral edge, which made a "tinging" noise as it was divided, so great was its tension. In some cases, as the last fibres of the muscle were divided, the plexus and artery sprang forward and were seen to lie quite freely. However, in all cases further exploration was carried out, as it was now an easy matter to see and feel if there was any posterior structure pushing the plexus forward. The field surveyed, exposure was obtained either by dividing the costo-cervical artery and depressing the subclavian, or, in those cases in which the latter arched high in the neck, by dissecting below it. Careful dissection usually disclosed one of the following structures angling the plexus upwards and forwards :—

1. A strong fibrous band running from the tip of the 7th transverse process of the 7th cervical vertebra to the 1st rib; this was found in 3 of the 4 cases showing either a long transverse process or a small bony cervical rib on radiography, and is presumably a 'fibrous cervical rib'. The difficulty was in distinguishing this from the next group.

2. Those in which there was a distinct thickening of Sibson's fascia. This thickening was variable, being either one or more discrete bands of hard tendinous fibres passing from the transverse process of 7th cervical vertebra down to the inner border of the 1st rib—hence the difficulty referred to above—but, more often, a broader fan of thickened tissue containing sharp bands of hard tendinous fibres or striped muscle tissue. On several occasions, this whole layer appeared felted as though it was the site of chronic inflammation, as described by Lewis and Pickering (1934), Eden (1939), and Aynesworth (1940).

Any band which was found together with the whole of Sibson's fascia was divided by cutting on to a Kocher's dissector. The apex of the pleura was then depressed, and a further examination conducted with the forefinger deep and the thumb superficial to the plexus to locate any bands which had previously escaped division. It must be emphasized here that the intention of the operation was, having as far as possible discovered the factor primarily responsible for the compression, to remove *all possible sources of compression irrespective of theory or individual finding.*

We classified the operative findings in our 20 cases into three groups, according to which factor appeared *mainly* responsible for the compression :—

a. Scalenus anterior muscle	5 cases (25 per cent)
b. Thickening of Sibson's fascia	10 cases (50 per cent)
c. A fibrous band from transverse process of C.7 to 1st rib, analogous to a fibrous cervical rib	5 cases (25 per cent)

In our opinion, however, no single factor is entirely responsible.

RESULTS

All the patients have been seen again recently, and follow-up varies from 24 to 6 months. Six months would appear to be the minimum satisfactory follow-up at the moment, for we have had two late relapses in the third and sixth post-operative months respectively. There were no operative or post-operative deaths, or morbidity. In analysing our results, patients were classed into one of three categories when they were seen on their last visit :—

a. Completely symptom-free	11 patients (55 per cent)
b. Very much improved, but showing some slight residuum of a trivial nature	5 patients (25 per cent)
c. Poor—anything other than the above	4 patients (20 per cent)

Of the last 4 patients, none were as bad as before operation: 2 were particularly interesting, being quite well till, in one case, six months after his operation, the patient had a spontaneous pneumothorax on the same side as his original pain. After this the pain re-started, and has remained ever since. On examination, his affected shoulder was considerably lower than the other, and he had a sharp upper thoracic scoliosis. He is now improving once again with physiotherapy and the scoliosis is decreasing. In the other case, the patient progressed satisfactorily until the third post-operative month, when, following extra heavy work—the patient had to nurse as well as support her invalid husband, the pain returned and has remained since. Of the 9 patients who had residual symptoms, 2 only remained with all their symptoms, but in the other 7 it was the pain in the forearm and fingers that remained resistant.

Of the 7 patients in whom Adson's test or abduction of the arm had materially altered the radial pulse, all had normal radial pulses after operation, including one patient classed as a failure. It was observed that the presence of pulse changes was not necessarily indicative of severe symptoms and signs.

Of the 10 patients showing wasting, only one showed it in a very severe degree (in fact, it was her main complaint), and although her pain was almost completely relieved by operation, her wasted muscles showed only partial recovery after ten months. Of 2 others with very definite wasting, one returned to normal and the other was considerably improved. Five of the 7 classed as having wasting of moderate or mild degree returned to normal. One was improved and one unchanged. Thus, it would seem that wasting is not always an irreversible process. In this respect, the total length of history appears to have less bearing on the prognosis than the length of time during which wasting has been present.

DISCUSSION ON AETIOLOGY

From an exhaustive review of the literature, one would think that every possible structure in the thoracic inlet and every possible mechanism that ingenuity could devise has been called upon to explain the symptoms of thoracic inlet compression. We hope to have shown by our operative findings that further observations are to be made, but though ingenuity be still alive, we fear that it cannot be taxed to provide one common formula to explain all the mechanisms of compression.

It would appear that from time to time very able descriptions have appeared of cases in which certain mechanisms were primarily responsible, and the authors have been able to show how alteration, usually surgical, of this mechanism has led to a greater or lesser degree of relief. It seems to us, however, that the danger has been in assuming that all, or even most, cases must be due to the same mechanism. In our own work, for example, we found some cases in which the scalenus anterior muscle was mainly at fault, some in which it was a fibrous rib, and others in which it was a thickening of Sibson's fascia. In very few cases did we feel that the most obvious factor was the complete mechanism. Also, we do not pretend that this would apply to all other cases.

Whilst it is true that cervical rib or thickening of Sibson's fascia, etc., could cause tension and angulation of the plexus or artery when the arm is depressed, and the scalenus anterior angulation when the arm is flexed and abducted, the effect on the cord is likely to be greater if the plexus or artery is gripped between the band or other abnormality behind, and the scalenus in front. The plexus or artery will be not only anchored and so less able to adapt themselves, but also chafed and irritated with each movement of the arm, so leading to an interstitial neuritis as was described in Blair, Davies, and McKissock's (1935) interesting post-mortem specimen. So much for the mechanism—a vice-like grip between the scalenus anticus in front and any firm structure behind, such as a cervical rib, a fibrous band, thickened Sibson's fascia, scalenus medius, or even an unusually shaped first rib. This would explain the fact that whilst most cases are improved by scalenotomy, a few show little benefit, because, despite the breaking of this vice, there may still be angulation or tension over the deep structure. This explanation unfortunately sheds no light on the aetiology, for, unless there is some precipitating factor, we would expect symptoms from birth in the case of true congenital abnormalities such as a cervical rib. We sought further information in the study of the individual features of the disease—particularly age, and side involved.

SEX, AGE, AND SIDE INVOLVED

All observers agree that there are more female cases than male (Adson and Coffey, 1927; Spurling and Bradford, 1938). The cases due to cervical rib show a higher female preponderance (Patterson, 1940), presumably due to the commoner occurrence of this anomaly in women.

Most patients fall into one of the two age groups (*a*) the larger, between 40 and 52; (*b*) the smaller, between 16 and 30. With these two facts in mind, observers in the past have dwelt on the drop of the shoulder-girdle as a main aetiological factor, stating that this is more likely to occur in women because of their poorer musculature, particularly if they are subjected to undue muscular strain at a time when the muscles are weak, e.g., the classical 'widows who take in washing'. The younger women who seem to develop symptoms are those who take on excessive work or are faced with the whole burden of running a home and looking after their small children.

If this were the whole story, we should expect that in a predominantly right-handed population the strain would be mainly taken on the right side, with an overwhelming preponderance of symptoms in that arm. This is not so, a high proportion of cases showing symptoms in the left hand only (Patterson, 1940; Spurling and Bradford, 1938), our own figure of 50 per cent left side only, as contrasted to 35 per cent right side and 15 per cent bilateral, being fairly typical. Two possible

explanations offered themselves: (1) That there is some anatomical abnormality predisposing the left side; (2) That the left arm is particularly used for some action that precipitates this syndrome. Whilst investigating this, we found that many patients had a slight scoliosis in the upper thoracic region, most commonly convexed to the right. This is a very normal occurrence in the population at large, and is generally attributed to the extra pull of the right arm

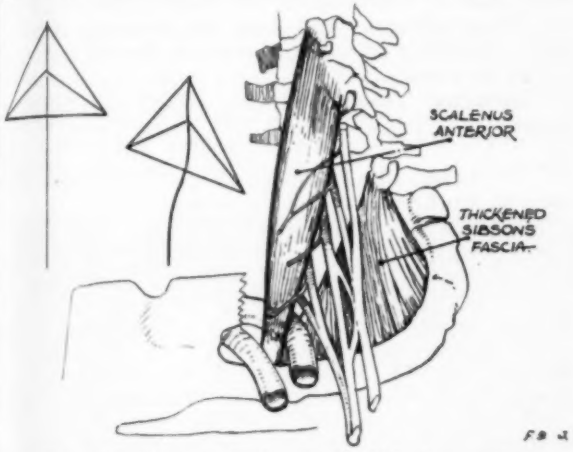

FIG. 148.—Diagram showing the brachial plexus and the subclavian artery passing between the scalenus anterior and thickened Sibson's fascia. The two small line diagrams show how this interval is narrowed by a tilting of the thoracic inlet.

muscles. On observation, this proved to be maximal in the upper fourth thoracic vertebræ, causing the first thoracic vertebra to be tilted to the left in a right-handed person. This means that the thoracic inlet will be tilted too, making the left first rib lower than the right, as seen in the exaggerated diagram (*Fig.* 148) and radiograph (*Fig.* 149). As a result, there will be a relative tightening of the scalenus anterior -Sibson's fascia vice, gripping the plexus and artery on the left as compared to the right. Sibson's fascia will be particularly stretched owing to its more extensive lateral attachment. Although this tightening will be much less than is shown in the diagrams, it would mean that any further fall in the thoracic cage will produce its first effect on the left, so that the left brachial plexus, being more firmly held, would be the more easily traumatized, even though the right arm is used much more. Thus, the incidence of symptoms will become more equally divided between the left and the right arms.

To test this, we observed a further series of cases :—

Of 6 with left symptoms only	5 had right scoliosis 1 had left scoliosis
Of 2 with right symptoms only	2 had left scoliosis
Of 4 with bilateral symptoms	2—no scoliosis 1—to right 1—to left

THE VASCULAR SYMPTOMS

Although we noted pressure against the subclavian artery in several of our explorations, in no case did the vessel appear to be either damaged or completely compressed. Perhaps this accounts for why we had no patients with major vascular disorders. On the other hand, ten patients complained of colour changes, including two with Raynaud-like phenomena. In all these cases, the colour changes were maximal in the fingers in which they complained of pain. In only two of these cases could the radial pulse be obliterated or markedly

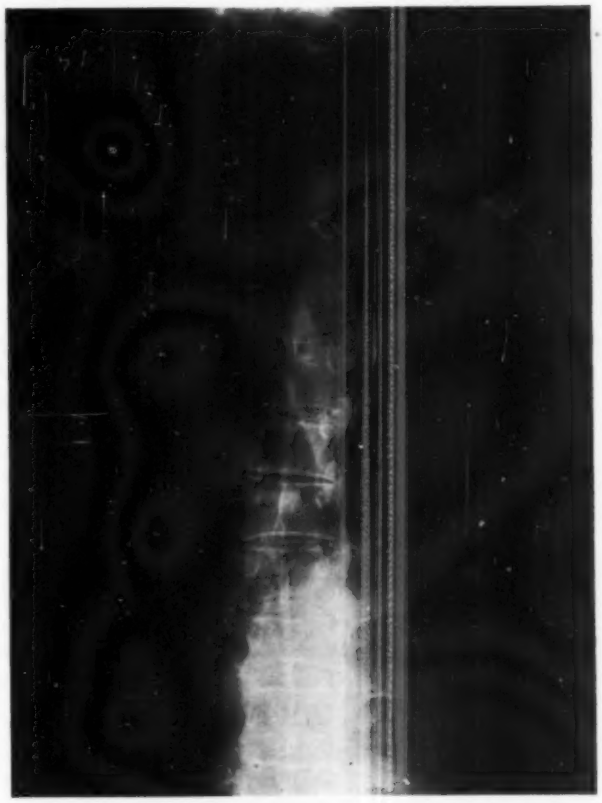

FIG. 149.—Radiograph showing tilting of the thoracic inlet due to scoliosis in this region. This is more pronounced than is usual.

diminished by posture of the arm or neck, and in neither case (nor in any of the other 8) did the manœuvre produce symptoms.

Combining the limited personal experience with the review of the literature has led us to the following belief: That the commoner phenomena of transient coldness and change of colour in the fingers are probably vasospastic in origin owing to irritation of the sympathetic nerves, probably as they run with the comparable somatic nerves in the brachial plexus. The major vascular phenomena, such as necrosis or gangrene of a digit or digits, are due to direct trauma to the artery leading to thrombosis and a superimposed element which may be either embolus formation or the vasospasm referred to above, for we find it difficult to credit that simple thrombosis of the subclavian artery could lead to vascular insufficiency in view of the excellent collateral circulation. It is possible that vasospasm could be reflex from afferent embolus in the irritated and damaged section of the artery. We have personal experience of division of the subclavian artery without any ischæmia resulting to the limb.

RESULTS

If all our above theories are correct, it is difficult to see why there should be any failures, whereas we had no less than 20 per cent. We suggest that the

most likely cause of failure, following correct diagnosis and adequate operation on the lines described above, is direct pressure on the nerves by the first rib, particularly if this is rotated so that they are caught over a sharp edge. Some late recurrences may be explained in this way too, postulating yet a further fall in the shoulder-girdle, as in our case described above. We are contemplating putting this to the test and excising part of the first rib. An interesting point for which we have at present no explanation is that, despite dramatic relief of symptoms immediately following operation, too early and too vigorous return to work seems to predispose to poor results. Incorrect diagnosis and functional overlay will of course exact their toll.

SUMMARY AND CONCLUSIONS

1. The typical picture of patients with thoracic inlet compression is presented and it is suggested that a positive diagnosis can be made in the absence of the so-called pathognomonic pulse changes—in fact, in some cases in the presence of symptoms only.

2. It is suggested that the mechanism of the production of symptoms is a gripping of the brachial plexus in a vice formed by the scalenus anticus in front, and a firm structure behind, usually a thickening of Sibson's fascia, but possibly cervical rib, bony or fibrous, scalenus medius, or even a normal first rib. It is further suggested that vascular phenomena are of two categories: (*a*) vasospastic, due to irritation of the sympathetic nerve; (*b*) thrombosis of the subclavian artery, due to direct trauma with superimposed vasospasm or embolism.

3. The aetiological factors in the production of the syndrome are suggested to be excessive work with the arm, particularly the movements of abduction and carrying, together with a drop in the thoracic cage, thus stretching and tightening the vice mentioned above. It is suggested that the normal scoliosis convex to the right in right-handed people will accentuate this mechanism on the left side.

4. Only a proportion of cases will require surgery —namely, those in whom other measures fail, those with severe symptoms, and those with wasting.

5. When surgery is required, it should consist of a careful exploration of the posterior triangle of the neck and division of *all* possible sources of compression.

6. A proportion of failures is to be expected, due to causes which are at the moment not clear. Too early return to heavy work should be discouraged.

APPENDIX

Since the above was written we have operated upon and followed up under the same conditions a further 10 cases. Their general clinical picture followed the same pattern as above. Of the 10 cases 6 were female, 4 male. The right side was affected in 7 cases, the left in 2, and 1 case was bilateral.

Operative Findings (11 Operations).—In 4 cases a thickened Sibson's fascia was mainly responsible.

In 3 the nerves were caught between a very tight scalenus anticus and a thickened Sibson's fascia.

In 2 there was a similar vice, but the posterior jaw was respectively a strong muscle, probably an unusual scalenus medius, in one, and a firm fibrous band in the other.

In 1 case the scalenus anticus seemed mainly responsible.

In 1 case having a rudimentary cervical rib no real cause of compression was found, the tip of the rib being well away and there was no obvious band, etc. Despite a complete operation she did badly, as might be expected.

Results.—Good, 6 cases; slight residuum, 3 cases; bad, 1 case.

We would like to thank all our colleagues who have so kindly referred cases to us.

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A SUBMUCOUS FIBROMA OF THE ILEUM CAUSING INTUSSUSCEPTION

By MURRAY T. PHEILS

INTESTINAL obstruction due to the intussusception of a benign tumour is an uncommon surgical emergency.

CASE REPORT

The patient, a female, aged 38, was admitted to St. Peter's Hospital, Chertsey, Medical Division, on Feb. 17, 1950, complaining of cramp-like abdominal pain for the previous two weeks. She was married and had three children. She stated that in the previous four years she had had several similar episodes of abdominal pain and vomiting, usually followed by diarrhœa. These attacks had lasted for from one to two weeks, and had occurred three or four times a year. During an attack two years ago she had had considerable pain situated in the right iliac fossa. On other occasions the pain had been in the umbilical region.

FIG. 150.—Straight radiograph of abdomen, showing several distended loops of small bowel.

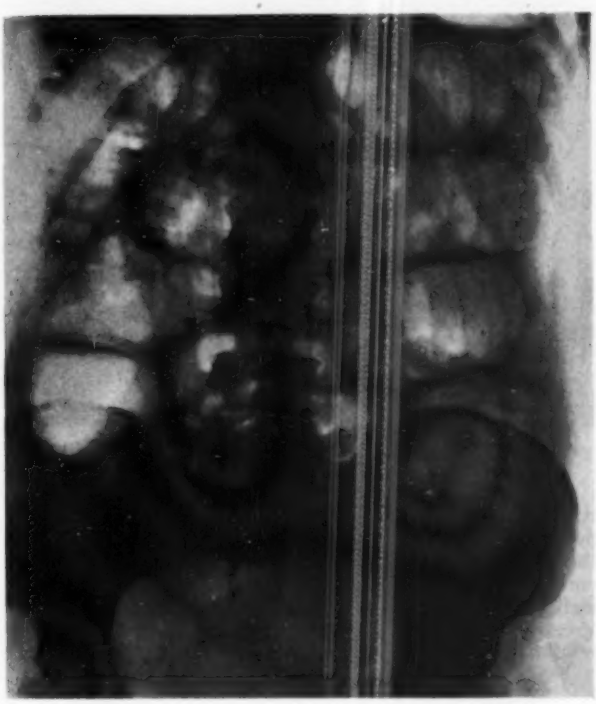

FIG. 151.—Radiograph showing further distension.

The present attack had gradually increased in intensity until her admission to hospital. Vomiting had started three days prior to admission, and had occurred four times. At first the vomit was a green colour, but later it was brown. For some days prior to the vomiting there had been nausea and anorexia. She stated that her abdomen had felt increasingly distended. She had had several loose stools three days previously, but since then she had not had her bowels open. Clinically the patient appeared remarkably well and cheerful. There was no clinical evidence of dehydration and the tongue was furred but moist. The abdomen was distended and there were increased bowel sounds. On rectal examination the rectum was empty and ballooned. Straight radiography of her abdomen showed several distended loops of small bowel (*Fig.* 150). Her pain settled down following admission and did not recur for a further 48 hours, when she vomited 22 oz. of dark brown material. A further straight radiograph (*Fig.* 151) of the abdomen showed a considerable increase in gaseous distension of the ileum and jejunum. A Ryle's tube was passed, and much dark brown material aspirated. On Feb. 22 she was transferred to the Surgical Division with a diagnosis of chronic small-bowel obstruction.

The patient's general condition remained excellent, but a further radiograph of the abdomen (*Fig.* 152) showed increased gaseous distension of the small intestine with fluid levels present. In view of the length of history and the patient's excellent condition, an attempt was made to relieve the distension by the passage of a Miller-Abbott intestinal tube. This was successful, and the small intestine was so satisfactorily decompressed that the tube could be removed on Feb. 26. The patient's fluid balance was maintained by suitable intravenous infusions. Her improvement continued until March 1, when she complained of a return of the abdominal pain. The abdominal distension also began to return, so the Miller-Abbott tube was re-inserted.

OPERATION.—Laparotomy was undertaken on March 3 under general anæsthesia—thiopentone, curare, nitrous oxide (Dr. F. G. Etheridge). A right paramedian incision was made, and on opening the peritoneum several distended loops of small bowel presented. An ileocæcal intussusception was delivered and easily reduced. The small bowel proximal to the intussusception was greatly hypertrophied, but there was no evidence of any strangulation. There was a tumour palpable at the apex of the intussusception about 2 ft. from the ileocæcal valve. About 5 cm. of bowel, including the tumour, were resected

and end-to-end anastomosis performed. The abdomen was closed in layers and she made an uneventful recovery.

PATHOLOGY.—The formalin-fixed specimen (*Fig.* 153) consists of a 4·5 cm.-long segment of small bowel, its average diameter being 2 cm. A small amount of mesenteric fatty connective tissue is attached to the serous surface. One centimetre from one cut edge, a roughly cylindrical piece of soft, pale-brown tissue projects from the serous surface, having measurements 1·2 × 0·7 × 0·3 cm. Its base disappears into a shallow pit in the bowel wall. The latter runs into the stalk of a pedunculated spheroidal tumour which projects inwards from the mucous membrane. The diameter of the stalk is 1·5 cm.

FIG. 152.—Radiograph showing decompression with Miller-Abbott tube in situ.

FIG. 153.—Photograph of specimen.

and it lies 1·5 cm. from the cut edge of the bowel. The tumour measures 2 × 3 × 2·5 cm. It is covered by pale-brown, velvety, finely nodular mucous membrane. Its cut surface shows a firm, pale-grey, 0·5 cm.-thick, outer portion covering a more yellow, softer, central portion which is studded with a small number of dark-brown spots. The mucous membrane of the bowel is congested in the neighbourhood of the tumour, but is otherwise normal.

HISTOLOGY.—The tissue is seen to consist of three layers. That covering the mucosal surface is made up of chronic purulent inflammatory granulation tissue (*Fig.* 154). Under this lies slightly infected, vascular, moderately dense, and cellular fibrous tissue (*Figs.* 155, 156). This layer is not clearly separated from the outer one, which is a looser and more mature fibrous connective tissue, showing patchy infiltration with chronic inflammatory cells. A preparation stained with Van Gieson's

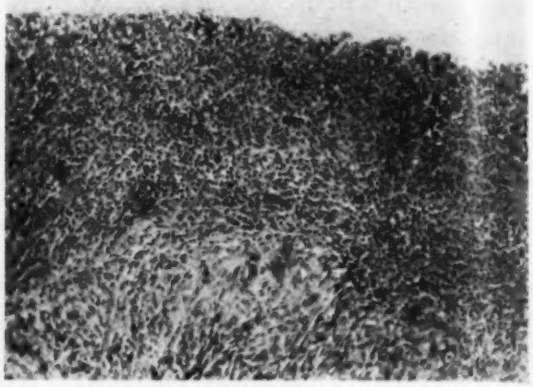

FIG. 154.—Chronic purulent inflammatory granulation tissue. (× 72.)

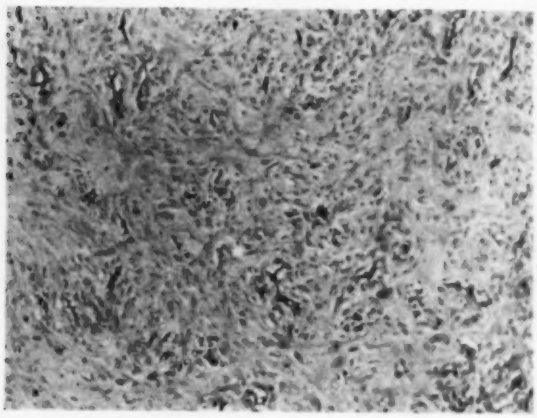

FIG. 155.—Cellular fibrous tissue, slightly infected, vascular, and moderately dense. (× 72.)

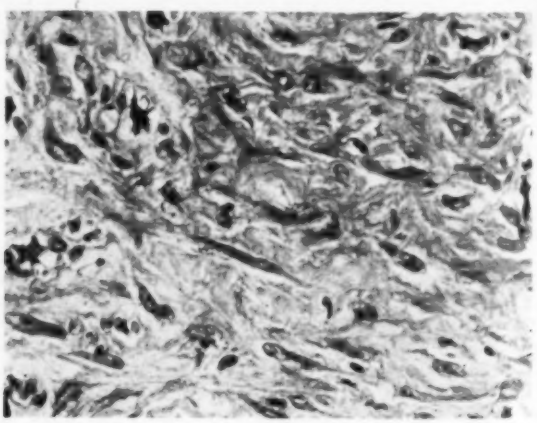

FIG. 156.—Higher power view of tissue in *Fig.* 155. (× 288.)

stain confirms that there is abundant collagen in the two outer layers; no smooth muscle can be identified with certainty. The tag of tissue on the outside consists of a loose, fibrous connective tissue.

The tumour appears to be a submucous fibroma. The presence of an active chronic inflammation confuses the picture, but the fibrous tissue is more abundant than would be expected for the degree of inflammation present, and no other tissue can be identified entering into the make-up of the pedunculated mass. The tag of tissue projecting from the outer coat is likely to represent a minor congenital abnormality. Its anatomical relation to the tumour suggests that it might have been an aetiological factor in the production of the latter.

DISCUSSION

Benign tumours of the small intestine are uncommon and seldom recognized before operation or autopsy. In a review of the literature, Lichtenstein and Dutra (1943) compile the following table of the location and character of these tumours :—

Type	*Duodenum*	*Jejunum*	*Ileum*	*Unspecified*	*Total*
Fibroma	2	4	10	1	17
Fibro-adenoma	1	—	—	—	1
Myoma and fibromyoma	8	10	15	4	37
Adenoma	10	8	14	—	32
Angioma	3	2	1	1	7
Lipoma	4	2	7	4	17
Neurofibroma	1	—	—	3	4
Osteochondroma	—	—	—	1	1
Total	29	26	47	14	116

In a review of 2434 autopsies Morrison (1941) found 21 tumours of the small intestine. These were 5 lipomata, 3 adenomata, 2 leiomyomata, 1 pedunculated subserous fibroma, 2 argentaffinomata, 4 adenocarcinomata, and 4 lymphosarcomata. Intussusception occurred in association with 2 lipomata and 1 adenomyoma. Dundon (1948) presented a group of 44 benign tumours of the small intestine. Two of this group had intussusception, 3 were incidental findings at operation, and 39 were found at autopsy.

From the series of small-intestinal tumours reported by Raiford (1932), Rankin and Newall (1933), and Weinberger and Paltauf (1948) benign tumours appear more likely to intussuscept than malignant tumours. Furthermore, intussusception appears to be the most common way for these tumours to present during life.

This patient probably had repeated attacks of intussusception over a period of four years. There was no evidence that this had at any time produced interference with the blood-supply of the bowel. On the other hand, the intermittent obstruction had produced a gross hypertrophy of the proximal intestine. The presence of active chronic inflammation in the specimen was also probably due to the trauma of the repeated intussusceptions. The tag of tissue on the serous surface of the bowel at the site of the tumour may possibly represent an attenuated Meckel's diverticulum. When first seen the patient appeared remarkably well in spite of an obvious intestinal obstruction. It seemed an ideal case for decompression by Miller-Abbott intubation, and undoubtedly the fact that this was successful made the operative conditions for the resection and anastomosis considerably easier.

SUMMARY

A case of intermittent small-bowel obstruction caused by the intussusception of a fibroma of the ileum is described. The literature and treatment by means of intestinal intubation and resection are discussed.

I wish to thank Dr. J. L. Pinniger for the pathological report and Mr. A. E. Clark for the photographs and microphotographs of the specimen; Dr. H. Gillespie for the X-ray photographs; and Mr. T. W. Mimpriss for critical help and permission to publish this case.

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IRREDUCIBLE INTUSSUSCEPTION IN INFANTS

BY MATTHEW WHITE AND WALLACE M. DENNISON, GLASGOW

JONATHAN HUTCHINSON reported the first successful operation for intussusception in an infant in 1871. At irregular intervals since then reports have appeared in the medical journals of one or two cases of successful primary resection for *irreducible* intussusception in infants. If resection and primary anastomosis *is* the method of choice in such cases, it is surprising that few of these authors report further successes from this method. Most surgeons with extensive experience with children have successfully performed resection and primary anastomosis on more than one occasion. Unfortunately these successful emergency resections are the exception rather than the rule. In most centres dealing with large numbers of cases of intussusception the mortality for resection and primary anastomosis in infants is between 70 per cent and 80 per cent (Herzfeld, 1939; Ladd and Gross, 1941; Gross and Ware, 1948). An exception to this high mortality is the series reported by Dennis (1947), in which he performed 8 resections with primary anastomosis, all patients recovering.

There can be little doubt that resection and primary anastomosis is the best form of therapy provided that the surgeon has extensive experience

of intestinal surgery in children. Whatever method is adopted, success will be rare unless one remembers that prolonged attempts at reduction will so exhaust the infant that further operative procedures will have little prospect of success.

Although admitting the advantages of resection and primary anastomosis, two large children's hospitals (The Children's Hospital, Boston, and the Royal Hospital for Sick Children, Glasgow) have adopted alternative methods of treatment. In Boston, Gross and his assistants (Gross and Ware, 1948) have adopted the aseptic Mikulicz resection; one surgical unit in Glasgow uses the method described by Parry in 1909 of short-circuiting the intussusception by performing a simple side-to-side anastomosis (usually an ileocolostomy), leaving the irreducible mass untouched (Rutherford, 1909; Montgomery and Mussil, 1930; Elliot-Smith, 1935; White, 1948; and Dennison, 1948). Gross and Ware report 14 cases treated by the Mikulicz technique, with 11 recoveries (mortality 21 per cent). The present communication is based on 16 cases of irreducible intussusception treated by ileocolostomy, with 12 recoveries—a mortality of 25 per cent.

Between 50 and 60 cases of acute intussusception are admitted to the Royal Hospital for Sick Children, Glasgow, each year, and the condition as seen in this hospital has been fully described elsewhere (MacFarlane, 1934; White, 1948; Dennison, 1948). In over 70 per cent the catastrophe occurs in the first year of life and the incidence of irreducibility varies from year to year. In the fifteen-year period between 1935 and 1949, 379 cases of intussusception were admitted to one unit of the hospital, and of these 29 were irreducible (7·6 per cent). Of these, 4 were moribund on admission, and at necropsy the intussusception was found to be irreducible; 9 were treated by resection, with 5 deaths—a mortality of 55 per cent. The remaining 16 cases were treated by simple anastomosis (*Table I*), and 5 of these have already been reported (Dennison, 1948). All patients in the series were very ill on admission and required correction of dehydration or blood-loss before operation.

Table I.—Cases treated by Simple Anastomosis

No.	Age	Duration	Primary Operation	Secondary Operation	Result
1	5 mth.	36 hr.	Anastomosis and exteriorization of mass	Intussusception reduced and returned to abdomen	Satisfactory
2	3 yr.	48 hr.	Anastomosis. Mass returned to abdomen	—	Satisfactory
3	7 mth.	120 hr.	Simple anastomosis	—	Died of shock
4	7 mth.	14 hr.	Simple anastomosis	—	Satisfactory
5	4 mth.	12 hr.	Simple anastomosis	—	Satisfactory
6	5 yr.	72 hr.	Anastomosis with drainage of abdomen	—	Satisfactory
7	4 mth.	24 hr.	Anastomosis and exteriorization	Laparotomy for small-bowel prolapse after two days	Aspiration of vomitus, collapse, and death
8	4 mth.	24 hr.	Simple anastomosis	—	Satisfactory
9	4 mth.	24 hr.	Simple anastomosis	—	Died of toxæmia 48 hours
10	4 mth.	72 hr.	Simple anastomosis	—	Satisfactory
11	10 mth.	120 hr.	Simple anastomosis	—	Satisfactory
12	6 mth.	12 hr.	Simple anastomosis	—	Died after 8 days. Bronchopneumonia
13	3 mth.	72 hr.	Anastomosis and exteriorization	Right hemicolectomy at two months	Satisfactory
14	8 mth.	?	Anastomosis and exteriorization	Local resection two days later	Satisfactory
15	3 mth.	36 hr.	Anastomosis and exteriorization	Local resection seven days later	Satisfactory
16	4 yr.	72 hr.	Anastomosis and exteriorization of gangrenous loop	Local resection after two weeks	Satisfactory

It will be seen from *Table I* that there is no constant relationship between the duration of the condition and irreducibility. The irreducibility is essentially a vascular catastrophe and may occur at an early stage. The consequent increase in mortality is not therefore entirely due to delay in diagnosis. If the mesentery of the cæcum and ascending colon has failed to become obliterated the cæcum is mobile and the apex of the intussusception is the ileocæcal valve, which advances along the ascending colon, dragging with it the cæcum, appendix, and terminal ileum. The extent of the travel depends largely upon the mobility of the colon, and the apex may reach the sigmoid or even the rectum, with relatively slight interference with the blood-supply. If, on the other hand, the normal process of obliteration

of the mesentery has taken place, the cæcum is fixed in position and the ileum is forced through the ileo-cæcal valve and advances at its own expense, with at first a changing apex. The mesentery of the ileum, however, soon becomes constricted as it enters the intussusception and the blood-supply is obstructed, with consequent œdema and congestion. The peritoneal surfaces of the inner and middle layers which are in contact become adherent and further advance is checked. In the first type with a lax mesentery and little vascular obstruction the intussusception may remain reducible for twenty-four or forty-eight hours or even longer. In the second type, vascular obstruction leads to œdema and congestion and reduction becomes impossible. The vascular obstruction eventually leads to gangrene of the bowel, but usually only the inner layer is affected and the ensheathing layer remains viable. Death occurs from intestinal obstruction and toxæmia, and we have never seen death from peritonitis in an *unreduced* intussusception. The return of the irreducible mass into the peritoneal cavity after a simple anastomosis does not therefore violate surgical principles. If the intussusception is forcibly reduced in such a case, the bowel may be so damaged that it never recovers and the patient may die of ileus or peritonitis. Even although the bowel shows no more damage than severe congestion, fæcal bacteria can be cultured from the serous coat (Ravitch and McCune, 1948). Although clinical peritonitis may not occur, this fact may explain the pyrexia which almost invariably follows successful reduction. Following forcible reduction, the entering and part of the ensheathing layer may be so devitalized that necrosis is inevitable and only resection will prevent perforation and fatal peritonitis. Prolonged attempts at forcible reduction usually lead to tearing of the serosa of the ensheathing bowel, and damage may be so extensive that exteriorization is obligatory. But whether the irreducible mass is exteriorized or whether, in suitable cases, it is returned to the peritoneal cavity, toxic absorption is inevitable and the infant remains seriously ill for several days.

When the 'irreducible' mass is returned to the peritoneal cavity one of three things may happen: it may pass as a slough (*Cases* 4 and 5); it may reduce itself; or it may fuse in situ and recanalize later (*Case* 6). In no case of this type have we seen any radiographic evidence of the short circuit two months after the operation. Only rarely can a definite diagnosis of irreducibility be made before operation, and only too often this complication comes as a very unpleasant surprise after the major part of the intussusception has been reduced without difficulty.

TREATMENT

If the infant is dehydrated or collapsed, resuscitative measures are adopted, but operation is never delayed more than an hour or two at the most. Dehydration or blood-loss are at least partially corrected before operation by infusion of saline, plasma, or whole blood.

Gas, oxygen, and ether have proved satisfactory in most cases, but cyclopropane has been valuable in seriously ill children. In two extremely ill babies satisfactory surgery was possible after procaine infiltration of the abdominal wall.

A stomach tube is passed and left in situ and the abdomen opened through a generous right rectus muscle-splitting or muscle-displacing incision. Reduction is accomplished as far as possible and the mass is then withdrawn from the abdomen and covered with hot saline packs to minimize heat loss from the exposed bowel. Only experience can teach the surgeon how long to proceed with attempts at reduction, but the experienced surgeon knows within a very few minutes if reduction will be possible. When he has decided that the intussusception is irreducible the anæsthetist is warned, the drip is speeded up, and a rapid lateral anastomosis performed between the ileum and ascending or transverse colon. If the bowel is of good colour and with an intact serosa or with only small serosal tears, the mass is returned to the abdomen. If there is any doubt about the viability of the bowel a cigarette drain is inserted. If the bowel is gangrenous it is fixed outside the abdomen after performing the anastomosis.

Post-operative Care.—Gastric suction is continued with an indwelling urethral catheter so as to keep the upper intestinal tract decompressed, and parenteral fluids are continued until the infant can meet its fluid and caloric requirements by oral feeds. The patients have been nursed in high-concentration oxygen tents, with excellent results. No dramatic improvements were obtained from the use of chemotherapy, but from recent experience aureomycin appears to be a life-saving drug in certain cases.

The rate and quality of the pulse are the main indices of the child's condition, and careful charting of the temperature, pulse, and respiration is done at hourly intervals until the patient is in a stable condition. Fluid balance is controlled by careful charting and by the study of the plasma levels of chloride, protein, and carbon-dioxide–combining power. Eucortone and D.O.C.A. have proved their value in the treatment of shock and toxæmia (Dennison, 1939).

When the irreducible mass has been exteriorized, resection is carried out as soon as the condition of the patient permits. On one occasion resection was necessary forty-eight hours after the primary operation owing to toxic absorption from the irreducible mass (*Case* 14). In *Case* 13 resection was delayed for two months.

SUMMARY

A series of 16 cases of irreducible intussusception treated by simple anastomosis is presented. The pathology of the irreducible intussusception is briefly reviewed. Only experience can dictate how long one can afford to spend trying to obtain reduction by manipulation and we would suggest that the surgeon should set a time limit for reduction. When manual reduction has failed, any further surgical procedures are fraught with danger. Whatever method is adopted one must expect a heavy mortality. When the ensheathing layer is viable it is justifiable to return the irreducible mass to the peritoneal cavity. When there is any doubt about the viability of the bowel the mass is exteriorized and resection carried out as soon as the condition of the patient permits.

Pre-operative preparation is important in all cases of intussusception. Post-operative care following the simple short-circuit operation includes the use of gastric suction, transfusion of plasma, and the nursing of the child in a high-concentration oxygen tent (Oxygenaire). Recently we have found aureomycin of value in combating toxic absorption.

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MALIGNANT CHANGE IN CHRONIC OSTEOMYELITIS

BY M. B. DEVAS

MALIGNANT change in chronic osteomyelitis has long been recognized as both a rare and late complication. Almost invariably the growth is an epithelioma which arises from the epithelialized lining of a chronic sinus. The tumours are of low malignancy and secondary spread is uncommon.

As the epithelioma may arise in the superficial or deep part of a sinus two clinical types may be recognized. Men are more commonly affected than women, and the tibia is the commonest site, as would be expected from the incidence of chronic osteomyelitis.

Diagnosis in the type of epithelioma occurring deep within the sinus is difficult clinically, but the features most frequently described are an increase in pain and discharge with increased swelling and hæmorrhage. Radiological examination shows in some cases an erosion and absorption of the bone and may indicate a true diagnosis.

In the superficial type, the same clinical features are observed, but the obvious presence of a fungating growth makes diagnosis simple and easily confirmed by biopsy.

The following case report is of interest in that it combines both superficial and deep types.

CASE REPORT

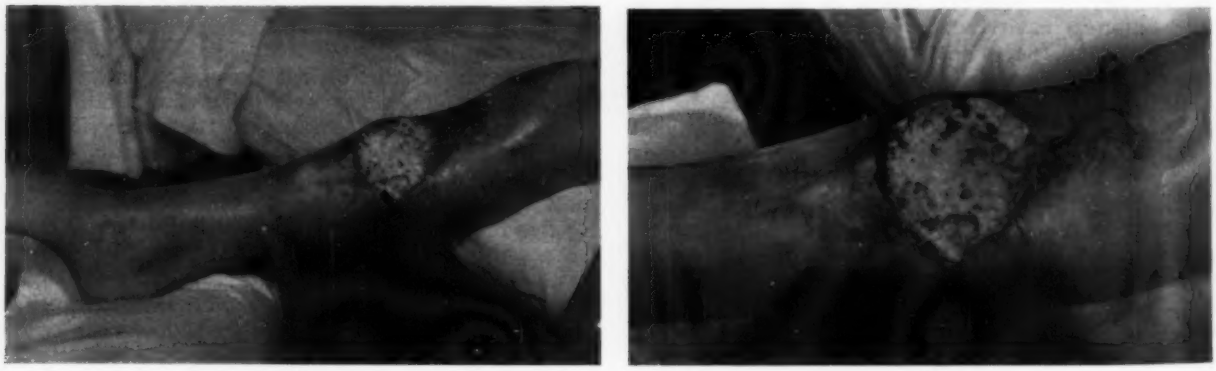
HISTORY.—A married woman, aged 56, was admitted to hospital with chronic osteomyelitis of the right tibia. Fourteen years previously, at the age of 42, she had a severe attack of acute osteomyelitis of the right tibia. Under treatment, in and out of hospital, for nearly two years, she was finally discharged with chronic osteomyelitis of the right tibia and a stiff right knee.

For the next twelve years the leg discharged continuously ; but ten months prior to her present admission it became very painful. Four months before admission some bone was discharged and the patient noticed ' proud flesh ' forming. Two attacks of bleeding, one severe, occurred.

ON EXAMINATION.—There was a large fungating mass, oozing pus freely, over the middle third of the right tibia and in the middle of a long scar. Towards the upper end of the scar there was an unaffected sinus (*Fig.* 157); the right knee was stiff. The lymph-glands in the right groin were enlarged and firm.

Radiological examination (*Fig.* 158) showed the whole of the upper shaft of the tibia to be affected with chronic osteomyelitis ; there was also cavitation of the bone under the site of the tumour.

A diagnosis of epithelioma arising secondary to chronic osteomyelitis was made and confirmed by biopsy, which showed squamous epithelioma with well-marked cell



A B

FIG. 157.—A, Showing the epithelioma on the anterior aspect of the right leg ; B, A close-view, showing the scar and sinus above the growth.

nests. Biopsy of the lowermost lymph-gland from the right groin was done at the same time, but showed only chronic inflammatory changes.

widely within the bone. The histological report was that : " The tumour is a well-differentiated squamous carcinoma with extensive keratinization ".

A B

FIG. 158.—A, Anteroposterior and B, Lateral, radiographs of the right tibia. The cavitation beneath the growth is shown well.

TREATMENT.—After a full course of penicillin, mid-thigh amputation was performed at the site of election and healing by first intention was obtained. The patient's general condition improved rapidly and the glands in the groin retrogressed. Six months after operation the patient had been fitted for her artificial limb, and the enlarged glands had disappeared from the groin.

FIG. 159.—The bisected specimen. The extent of the growth is clearly shown. From the plane it seems surprising that a pathological fracture has not occurred.

SPECIMEN.—After fixation in formalin the limb was bisected (*Fig.* 159). It was then obvious that the cavitation seen in the radiograph was due to tumour tissue eroding

DISCUSSION

In this case chronic osteomyelitis existed for fourteen years prior to the onset of malignant change. It is noteworthy that the symptoms of increased pain probably marked the early stages of the growth of the epithelioma deeply, but the superficial part of the tumour did not show until a few months later.

Recently Marks and Turner (1949) published 3 cases (occurring in the thigh), and McAnally and Docherty (1949) 9 cases, of malignancy in chronic osteomyelitis. In the latter series two cases showed secondary spread, one of which was from the hand, as was the case of Stewart, Obermayer, and Woolhandler (1940). However, metastatic spread is recognized to be both rare and late, Bereston and Ney finding only 7 cases in 1941, to which they added 2 of their own.

Most cases occur in the tibia, 8 out of 12 of Benedict's (1931) cases being in that situation.

Henderson and Swart (1936) had one case in which a fibrosarcoma coexisted with an epithelioma ; McAnally and Docherty had a case which was at first given a similar diagnosis, but later proved to be only an epithelioma simulating fibrosarcoma in some parts.

Amputation is the usual treatment and where secondary spread is not present the prognosis is excellent.

SUMMARY

A case of malignant change in osteomyelitis is described occurring in a woman. There was no metastatic spread and mid-thigh amputation was performed.

I wish to thank Mr. B. Whitchurch Howell for permission to publish this case; and Dr. L. W. Proger and the Royal College of Surgeons for the histological report and the photograph of the specimen.

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MULTIPLE PAINFUL GLOMUS TUMOURS

BY TOM ROWNTREE, SOUTHAMPTON

HISTORICAL

IN 1740 Cheselden described three patients, of whom two suffered from an exquisitely painful little tumour on the shin, and the third from one on the buttock; each patient was relieved by removal of the tumour. Wood in 1812 described a similar condition and called it " painful subcutaneous tubercle ". About twenty examples were subsequently reported under the same term, but their exact nature is in doubt owing to lack of histological examination. Many of them must indeed have been glomus tumours (angioneuromyoma or glomangioma), but the clinical picture is so like that of several other conditions, notably cutaneous leiomyoma (Stout, 1937), that confusion is bound to have arisen, and no case reported before 1924 can be accepted under the diagnosis of glomus tumour.

Masson in that year drew attention to a tumour he had observed on the finger-tip, and he demonstrated its origin from the subcutaneous glomera. Since then many cases have been reported; Ottley (1942) and Beaton and Davis (1941) have fully reviewed the literature; Popoff (1935) has described in detail the histology of the normal glomus and of its tumours.

Masson (1924) stated that glomangiomata always occurred on the finger-tips; but as Mackey (1948) pointed out, the lower limb is affected as often as the upper. The finger-tip is the usual site in the upper limb, but in the lower limb the distribution is more proximal. Masson and many other authors have suggested that glomus tumours are always solitary; there is, however, no reason why multiple tumours should not occur, and indeed the following case is an example. The reason for reporting it is that it shows, in common with all other reported cases of multiple painful glomus tumours, one feature which I believe is not generally known and which has not hitherto been recorded.

Painless glomus tumours have also been described, and they are sometimes multiple (Weidman and Wise, 1937). What determines that some should be painful and some painless is not known; Slepyan (1944) described a case in which the two types coexisted. I am not concerned here with the painless variety.

CASE REPORT

A healthy electrician, aged 25 (born in 1923), began in 1941 to complain of intermittent severe pain in the right popliteal fossa. During his military service he often attended the sick-parade and was treated by all the methods customarily used for localized unexplained pain. He was given injections, radiant heat, massage, and he was even suspected of malingering. The pain later became constant, with accesses of sharp stabs brought on by prolonged standing and by pressure, but it did not keep him awake. The pain was always in the same site

FIG. 160.—Photograph of the back of the patient's leg to show: (*a*) The site of the tumours. The lower cross marks the site of the first two tumours and the upper cross marks the site of the third tumour. (*b*) The shape of the incision used, the S-shape giving a better exposure and being less likely to cause a contracture than is a straight incision.

without radiation; he had no tingling or other sensory disturbance and no motor loss, but he noticed that the right leg, over the course of the past few years, had wasted slightly.

In 1936 he sustained a fracture of the lower end of the left tibia and fibula, which recovered with no residual disability. There was otherwise nothing relevant in his past or his family history.

He first attended the Royal National Orthopædic Hospital in September, 1948. Examination showed no abnormality apart from the right lower limb. The thigh and the calf were wasted about 3 cm. each. The passive movements of all joints were full and painless, but, unless the knee was flexed, dorsiflexion of the ankle was limited by pain in the popliteal fossa. Voluntary power was normal.

Close inspection of the painful area revealed a tiny telangiectasis at the lower angle of the popliteal fossa; deep to it was the suggestion of a small swelling, but the exquisite tenderness prevented accurate palpation. The tenderness was entirely localized and produced no peripheral tingling. Further examination revealed another tender spot at the upper angle of the popliteal fossa (*Fig.* 160), although no tumour could be felt there, and no telangiectasis was seen. No objective sensory changes and no vascular changes were found.

DIAGNOSIS.—The tender spots lay in the line of the medial popliteal nerve, and so nerve-sheath tumours or neurofibromata were suggested; but there was no interference with conduction in the nerve and no subjective sensory change. Moreover there were no other tumours or abnormal pigmentation elsewhere. The exquisite tenderness suggested painful glomus tumours, and this was the pre-operative diagnosis.

OPERATION.—The tender spots were marked with ink before the induction of the anæsthetic. In a bloodless field, an S-shaped incision was made in the right popliteal fossa (*Fig.* 160); each of the two curves of the incision was centred on one of the two ink-marks. The lower semicircular skin-flap was raised, and after careful search in the subcutaneous fat a small grey-brown tumour, 7 mm. in diameter, was removed from a point exactly underlying the mark on the skin. Further dissection under the deep fascia at the same level brought to light a second identical tumour.

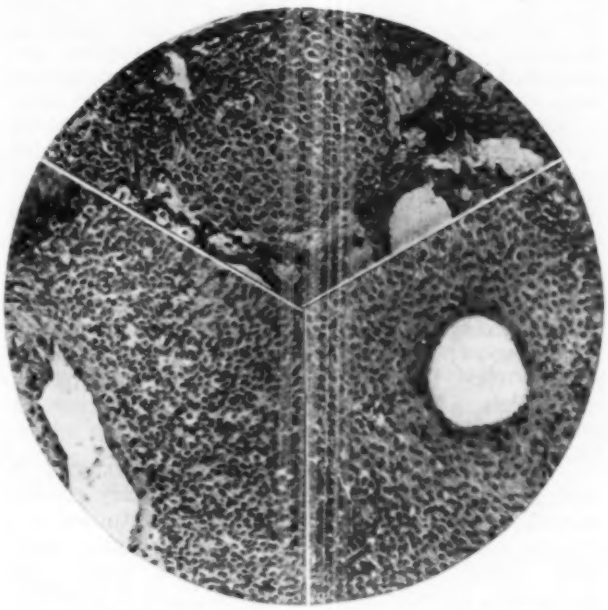

FIG. 161.—Microphotographs of the three tumours, showing a mass of characteristic glomus cells. (× 240.)

The upper flap was now raised, and, in the expected situation this time under the deep fascia, a third tumour, exactly like the first two, was found.

Table I.—MULTIPLE PAINFUL GLOMUS TUMOURS
(INCLUDING LOCAL RECURRENCES)

No.	Author	Date	Sex	Number of Tumours	Site	Remarks
1	Picard	1931	M.	2	Left index finger	
2	Adair	1934	?	4	Forearm	
3	Plewes	1941	M.	2	Right little finger	
4	Slepyan	1944	M.	2	Right forearm	Also had 12 painless tumours scattered on the trunk
5	Thomas	1933	M.	2	Left thigh	
6	Stout	1935	F.	2	Heel	
7	Bergstrand	1937	M.	Many	Right foot	The only described case of intra-osseous glomangioma
8	Bergstrand	1937	M.	3	Right ankle	Three further recurrences after removal of the first three tumours
9	Mulazzi	1940	M.	2	Ankle	Second tumour appeared 3 cm. away from the scar of removal of the first
10	Paes, Chaves, and Machado	1943	F.	7	Left lower limb	Appeared in succession over the course of a year
11	Frykholm	1945	M.	3	Right ankle	
12	Rowntree	1950	M.	3	Right popliteal fossa	Present case
(13	Mulazzi	1940	F.	2	Right ankle	Second tumour developed in the scar of the operation for removal of the first)

The wound was closed and the patient made an uninterrupted recovery. He remained comfortable until January, 1950, when he began to complain of pain in the right shin. But exploration on March 23, 1950, revealed no abnormality apart from some slight periosteal thickening. Recovery was uneventful, and he is now altogether free from pain. He was last seen on May 3, 1950.

PATHOLOGY.—It was suggested by an onlooker at the operation that the tumours were lymph-nodes; the surgeons themselves were surprised at the number of tumours. But the histology leaves no doubt about the diagnosis; one of the striking features of the histology is the exact similarity of all three tumours. I am indebted to Dr. H. A. Sissons for the following report: "Each of the three tumours has the characteristic histological structure of a glomangioma, consisting of masses of palely-staining 'glomus' cells which are often arranged around conspicuous vascular spaces. The microscopic appearance of the three lesions is remarkably similar." (*Fig.* 161.)

DISCUSSION

The present case is the twelfth reported example of multiple painful glomus tumours. Solitary glomus tumour is not excessively rare. I have studied 123 reports published in various languages since 1924, each report describing at least one case. The proportion between multiple and solitary is therefore less than one in ten.

In the published cases (*Table I*), the lower limb was affected more often than the upper. In all of them the histological proof of the diagnosis was available, but in one, in addition to two painful tumours on the forearm, there were twelve painless tumours scattered on the trunk (Slepyan, 1944). In two cases the second tumour appeared after removal of the first. In fact Paes' patient (Paes, Chaves, and Machado, 1943) developed seven tumours in succession over the course of a year, each tumour after removal showing the typical histology. Mulazzi's (1940) first case developed the second tumour a few centimetres away from the scar of removal of the first, and was possibly a recurrence rather than a new independent tumour. There were two examples of local recurrence of tumours—Bergstrand's (1937) and Mulazzi's second case.

All the patients, including the present one, showed an important common characteristic. In each the painful tumours were grouped close together, an occurrence not, I believe, hitherto described. I have found no recorded instance of multiple painful glomus tumours that were scattered. In only one case were the tumours more than 6 in. apart—a female in whom (Paes) all the tumours were on the same lower limb, the highest at the top of the thigh and the lowest in the calf.

To know of the focal distribution of multiple painful glomus tumours is of practical importance, because the presence of only one tender spot may not indicate a solitary tumour; very careful palpation in the neighbourhood is necessary in the examination of all cases to avoid missing second or even third tumours. Moreover, during operations to remove glomus tumours, it is necessary to search under the deep fascia, even though one tumour may already have been found in the superficial fat.

I thank with pleasure Mr. H. J. Seddon for permission to publish this case and for his encouragement. It is also a pleasure to thank Dr. Sissons for the pathological report and for the fine microphotographs.

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BENIGN CYSTIC TERATOMA (DERMOID CYST) OF THE TESTICLE

BY IAN MUIR

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BENIGN cystic teratoma is the rarest tumour of the human testicle. Cairns, in a Hunterian Lecture delivered in 1926, could find only 47 cases recorded in the literature; Dockerty and Priestly (1942) found 3 cases out of 400 testicular tumours seen at the Mayo Clinic between 1907 and 1942; and Hickinbotham (1950) discovered no case in a review of 95 tumours treated at the United Birmingham Hospitals between 1936 and 1946. In the horse the disease is not uncommon and seems to have a frequent association with undescended testicle, a finding which is rare in man. Its grotesque appearance has always endeared it to the collectors of surgical curios, while its peculiar features have provided both clinicians and pathologists with matter for speculation; much of this has been highly imaginative and correspondingly unfruitful, but the more rational hypotheses have contributed to the knowledge of the

general problem of tumour formation. The most obvious feature of the lesion is the cyst filled with hair and creamy sebaceous material, and this has earned for it the title of 'dermoid cyst', a title which, however, may be misleading, for the microscopical examination of these lesions determines them as true teratomata comparable with those occurring in the ovary, the sacrococcygeal region, the anterior mediastinum, the base of the skull, and, more rarely, in the neck and retroperitoneal region.

Where sufficient details are available the literature shows that benign cystic teratoma of the testicle is always first noticed at or soon after birth; in one of the earliest papers on the subject Wilms (1896), reviewed 17 cases and recorded the age of the patient when the disease was first noticed in 11; 4 were noticed at birth, 4 shortly after birth, and 3 in the early years of life. It can therefore be stated with certainty that these tumours are congenital, their origin probably being at an early period of intrauterine life. Apart from the mechanical effects of their size, they cause no symptoms, so that cases frequently do not present for advice until adult life, even though the swelling may have been observed in childhood; thus four of Wilms's cases were 32, 34, 39, and 42 years of age when they came to operation.

The tumours arise in the body of the testicle and, as they expand, the testicular tissue is compressed until it sits like a cap on the eminence of the tumour. Occasionally the tumour may become pedunculated and apparently separate from the testicle, a fact which led some observers to claim that the tumour had an extra- or peritesticular origin (Verneuil, 1855; Bland-Sutton, 1922), but Wilms (1896), by careful review of previous cases and study of one of his own, showed that the tunica albuginea and the tunica vaginalis could be seen to enclose both tumour and testicle without interruption and that the lesion was in fact intratesticular. A few cases have been reported as occurring in the epididymis or rete testis, but this is exceptional (Willis, 1948).

In structure, the benign cystic teratoma of the testis is similar to its more common counterpart occurring in the female gonad—the well-known ovarian 'dermoid'. The most obvious feature is the skin-lined cavity containing hair, which is often single, but may be represented by two or more similar cysts, while the solid part of the tumour is either disposed more or less evenly around the cyst or aggregated at one pole, where it projects into the cavity of the cyst as the so-called germinal bud. Microscopical examination shows the presence of adult and well-differentiated tissues of all three germinal layers lying together in haphazard fashion and frequently aggregated in the germinal bud. The cyst wall is composed of stratified squamous epithelium with its appendages of hair and sebaceous and sweat glands. As in the case here described, an attempt at organ formation is sometimes suggested by the finding of respiratory epithelium and cartilage in association and alimentary mucous membrane surrounded by smooth muscle. Teeth are not uncommonly discovered (Bland-Sutton, 1922), and an even more elaborate organization in the form of a loop of bowel has been described (Murray, 1913). The predominance of the skin component of these tumours seems to be due to the propensity of the skin to grow hair and to secrete sebum while the other glandular elements remain relatively dormant. Sometimes, however, cysts are lined by other types of epithelium and contain a corresponding secretion, such as mucus, cerebrospinal fluid, and so forth. Benign teratomata have been described where the skin element is completely absent and the tumour solid or containing a number of small cysts (Wakeley, 1938); this variation is due only to a fortuitous selection of tissues, and there is no essential difference between this type of tumour and the more common dermoid type.

The behaviour of these tumours is essentially benign, and although many of the published cases did not present for treatment until well on in adult life, no well-established case of malignant change has been recorded. Malignant change in a previously benign 'dermoid' teratoma of the ovary is well known, and it may be that absence of its occurrence in the testicular form is explained only by the rarity of the latter and the incompleteness of some of the earlier records.

CASE REPORT

J. R., aged 21 years, was referred to the Out-Patient Department of the Surgical Professorial Unit by Dr. A. E. Campbell, of Smethwick, with an enlargement of the right testicle. This had first been noticed by his father when J. R. was 3 years old, but it had caused no inconvenience and nothing was done about it until he was called for medical examination for service in His Majesty's Forces, when the enlargement of the testicle was noted and he was advised to consult his doctor.

ON EXAMINATION.—The upper part of the right testicle was found to contain a cystic swelling 2 in. in diameter. The lower pole of the testicle, epididymis, and cord were normal, as were the testicle, epididymis, and cord of the other side, and general examination showed that he was an otherwise healthy young man. Radiography of the chest was normal.

Removal of the testicle was advised and on Aug. 12, 1950, he was admitted to the Surgical Unit under the care of Mr. B. N. Brooke.

AT OPERATION.—Orchidectomy was performed under general anæsthetic on Aug. 15. His post-operative course was uneventful and he was discharged home on Aug. 26.

The Specimen.—Externally the testicle was enlarged, but the SURFACE was intact and of normal appearance. On section it was found that the upper two-thirds of the testicle were replaced by a cyst 5 cm. in diameter. The cyst was tightly packed with hair and sebaceous material, and, when this was removed, it was found to be lined by white skin from which hair was growing. This lining was thrown into low folds and projections in places, but there was nothing that resembled a germinal bud. The wall of the cyst was of uneven thickness, varying between 2 mm. and 5 mm., the thickest parts being at the lower pole and on the equator at the anterior aspect. Above and at the sides the cyst wall blended with the tunica albuginea, while below, where it was most thick and the growth of hair most dense, it lay in direct contact with the testicular tissue. The testicular tissue of the lower pole, the epididymis, and cord showed no abnormality.

Microscopical Report (by Dr. J. G. Jackson, of the Department of Pathology, University of Birmingham).—*Histology*: The cyst is lined by hyperkeratotic, stratified squamous epithelium, which in places projects in papillary form into the cavity. Hair follicles, sweat glands of apocrine type, and a large number of sebaceous glands are present. Numerous bundles of smooth muscle are present in the connective tissues beneath the

epithelium. The general arrangement of these structures is that seen in the skin, although they are very abundant in this tumour.

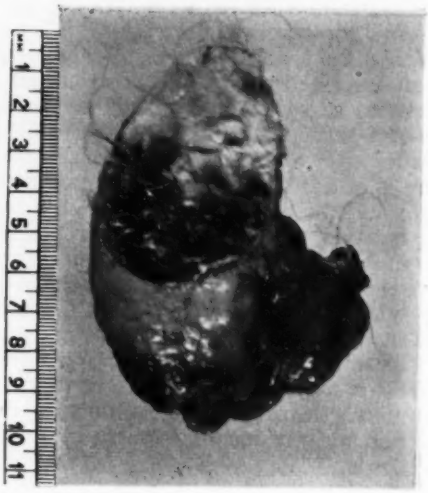

FIG. 162.—The testicle has been incised down its anterior border and the hair and sebaceous material filling the cyst can be seen.

FIG. 163.—The testicle has been divided into two, and most of the hair removed from part of the cyst.

FIG. 164.—The stratified lining of the cyst is shown and keratinization can be seen. This photograph shows hair follicles cut in section and sebaceous and sweat glands.

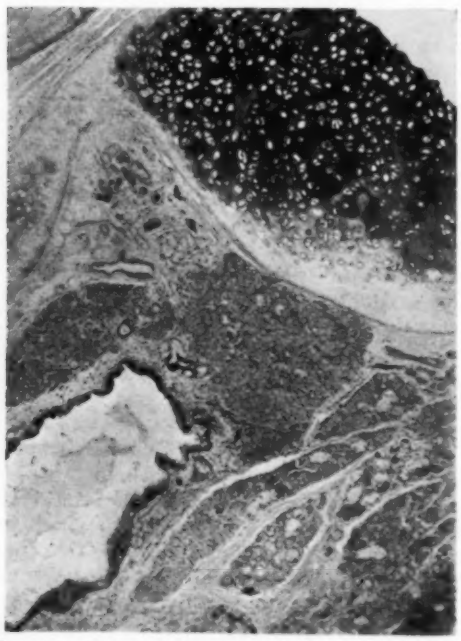

FIG. 165.—Above and on the right can be seen an area of cartilage; below and on the left is a cavity lined by ciliated columnar epithelium of respiratory type; between this and the cartilage are numerous acini, some serous and some mucous, suggestive of a bronchial gland structure.

Externally the tumour has a dense fibrous capsule, and between this and the skin lining of the cyst there are areas of sclerosing lipogranulomatous reaction, possibly the result of sebaceous material escaping into the wall of the cyst.

Elsewhere in the wall there are irregular channels lined by columnar epithelium of respiratory type. In relation to these structures there are glandular lobules with the structure of serous and mucous bronchial glands, and also nodules of well-formed cartilage.

In another part there are cavities surrounded by smooth muscle cells and lined by columnar epithelium of intestinal type, with goblet cells and Paneth cells within deep invaginations from the surface. One of the larger of these cavities is filled by granular debris infiltrated by large numbers of neutrophil polymorphonuclear leucocytes. The epithelium lining this cavity has been largely replaced by cellular granulation tissue and there is an accumulation of foamy macrophages around it.

DISCUSSION

The tumour described therefore contains well-developed tissues of all three germinal layers in a high degree of differentiation and is to be classed as a benign teratoma similar to those described previously by other authors (D'arcy Power, 1887; Jackson Clarke, 1896; Bland-Sutton, 1903; Barrington, 1910; Hughes, 1911). There had been no

pre-operative evidence of inflammation and the polymorph infiltration noticed in one area was thought to be the result of sebaceous material having passed into the wall of the cyst. A striking similarity exists between the benign teratomata occurring in the testicle and those in the ovary and other sites (anterior mediastinum, base of the skull, sacrococcygeal region, and neck) and any satisfactory theory of their causation must explain their occurrence in all these sites. Minor differences do exist—for instance, the sacrococcygeal tumours tend to show a higher degree of organization than those in the gonads—but the similarities far outweigh the differences.

The original view of the formation of testicular dermoids was propounded by Verneuil in 1855, and later found a staunch adherent in Bland-Sutton (1922)—namely, that the tumour represented an imperfect or suppressed fœtus, imprisoned by the tissues of the completely developed organism—so-called twin inclusion or fœtus-in-fœtu. To support this it was necessary to postulate some form of parthenogenesis from an early multipotent germinal cell. This view has been strongly challenged by Willis (1935 and 1937), Nicholson (1929 and 1930), and others, who point out that in spite of the occasional discovery in teratomata of formed structures such as teeth, digits, and even a loop of bowel, it is impossible to discover any general arrangement or grouping of parts such as might be expected if the malformation did represent an imperfectly formed fœtus. It is true that various tissues can be found in a relationship akin to that in the complete organism; thus in the case described, cartilage is in close association with respiratory epithelium and mucous membrane is surrounded by smooth muscle, but there is no general axial arrangement indicative of fœtal formation, as can be found in even the most deformed and amorphous embryos. Some authors have indeed described fœtal arrangement, but the findings have failed to stand up to a more critical and dispassionate examination.

Subsequent studies in experimental embryology threw new light on the problem and suggested an explanation more consistent with the facts. It was shown (Spemann, 1927) that the orderly development of the tissues of the embryo depends not on the inherent propensities of the embryonic cells and their predestination for a particular germinal layer or tissue, but on the action of certain unidentified substances which were called organizers. Thus, if in the early embryo a piece of primitive skin ectoderm is exchanged with a piece of brain ectoderm in the same or a different embryo, the transplanted tissue will develop in conformity with its new environment. Similarly, if pieces of ectoderm and mesoderm are interchanged, they will develop the normal characteristics of the tissue into which they have been transplanted. Furthermore, it was demonstrated that the region of the dorsal lip of the blastopore contains a substance which controls the axially disposed development of the whole organism and which has been called the primary organizer, the other organizers, acting more peripherally in regions and tissues, being designated as secondary.

In the case of teratomata it is suggested (Needham, 1936 and 1942) that a group of cells becomes cut off in some way from the influence of the primary organizer, while secondary organizers continue to exert their effects, thus producing a conglomeration of well-differentiated tissues but without any segmental or axial arrangement. Why the lesions should occupy certain positions is not yet clear, although it has been suggested that the sites of teratomatous formation are all, at some period of development of the embryo, close to the position of the primitive streak.

SUMMARY

The features of benign cystic teratoma of the testis—often called dermoid cyst—are described. The tumour is congenital and remains benign.

A typical case is recorded.

The two main theories of causation are discussed and disturbances of action of embryonic organizers are thought to provide the most adequate explanation.

I am grateful to Mr. B. N. Brooke for his advice and his permission to publish this case, which was treated under his care; to Dr. J. G. Jackson for his histological report and for the photomicrographs; to Miss B. Smith for the colour photographs; and to Miss M. Hollier for her secretarial assistance.

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A TECHNIQUE OF PARTIAL GASTRECTOMY

By T. O'NEILL, Dublin

WHATEVER may be the subsequent effects, the cardinal upset in gastro-intestinal rhythm following gastrectomy appears to be the precipitate entry of food into the jejunum. The objective of the operation described is to ' break ' the flow into the jejunum without producing intestinal obstruction. A central stoma is made with an upper and lower valve; the lower one is the larger and the more important of the two.

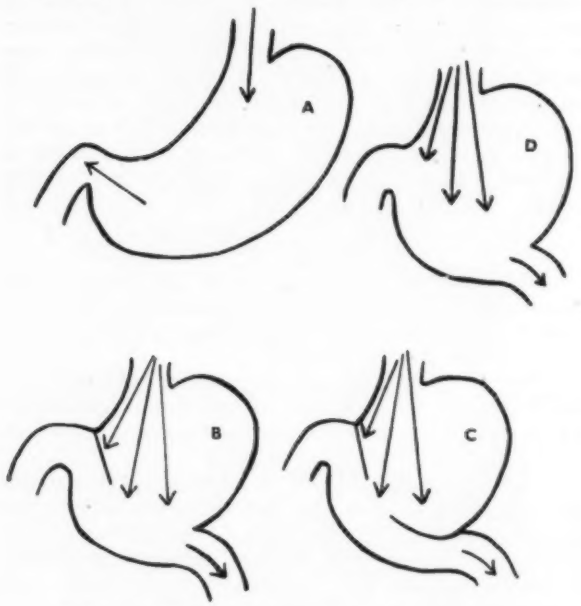

FIG. 166.—Diagrammatic representation of passage of food through stomach: A, Normal stomach. B, Effect of Finsterer valve in modifying the passage of food from the œsophagus to the jejunum. C, Effect of double valve described in text. D, Passage of food from œsophagus to jejunum following Polya gastrectomy.

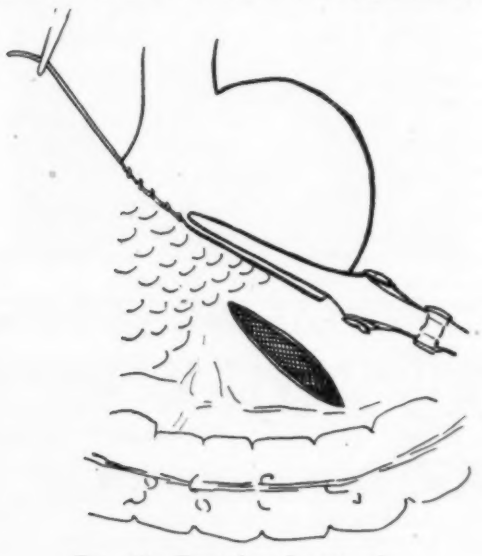

FIG. 168.—Formation of upper valve.

In an excellent paper, Wakeley (1947) illustrates twelve different types of partial gastrectomy; the plea for publication of a further modification is that it is considered to produce less functional disability than do other operations of the Billroth II type (O'Neill, 1950). Since publication of that article one of the cases reported as symptom-free has suffered periodic attacks of severe dumping.

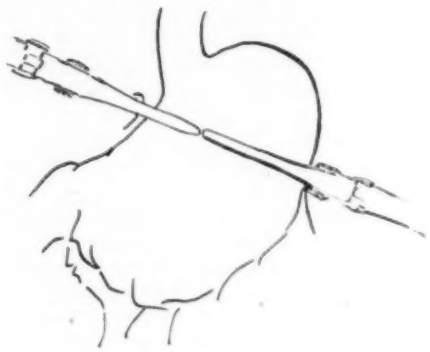

FIG. 167.—Payr's clamps in position.

OPERATION

A finger is pushed into the lesser sac at about the level of the middle of the greater curvature; unless the patient is thin no effort is made to keep between the stomach and the right gastro-epiploic artery. The division of vessels proceeds towards the left; when the left gastro-epiploic artery is reached the vessels are ligated in all circumstances between the stomach and the artery. Even when a high resection is not envisaged, the operation is made easier by tying the vasa brevia until only one or two are left.

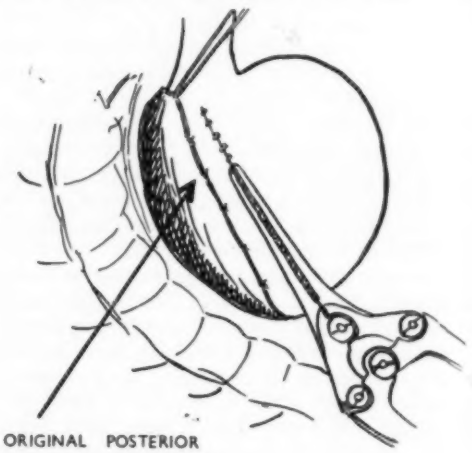

FIG. 169.—The upper valve has been formed and the mesocolon has been sutured to the posterior wall of the stomach. The point representing the posterior corner of the rent in the mesocolon is shown as opposite the tip of the Payr's clamp.

On continuing the ligation to the right, a new plane of separation is reached, between the anterior layer of the great omentum and the right layer of the lesser sac. The anterior layer is divided between forceps

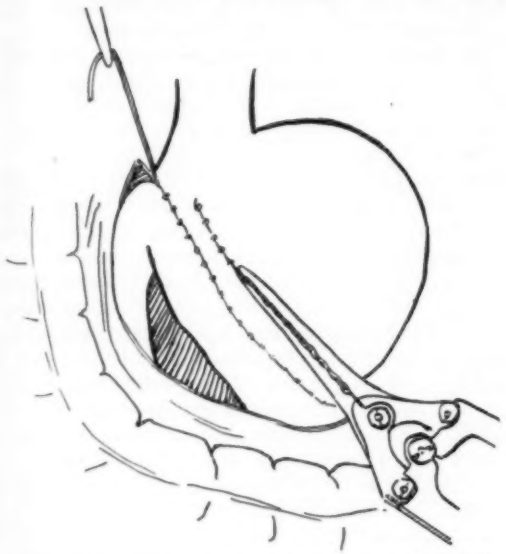

FIG. 170.—The seromuscular gastrojejunal suture line has been inserted.

to a little past the pylorus; the avascular posterior layer is divided with the scissors. The right gastro-epiploic artery is thus exposed and is clamped and

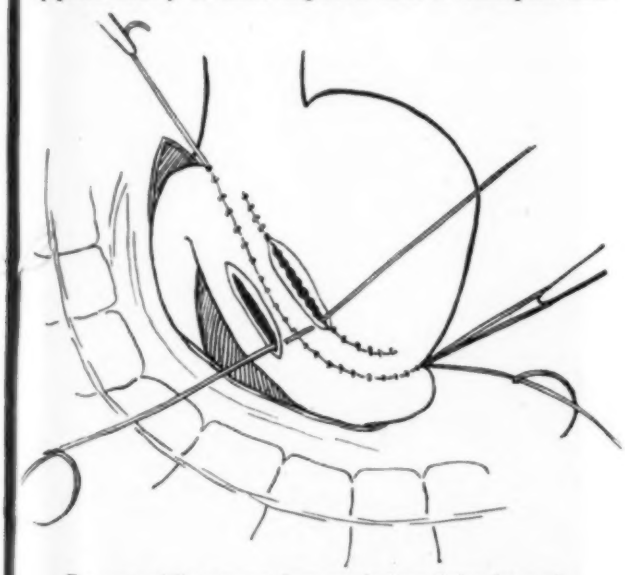

FIG. 172.—The stoma; hæmostatic layer being inserted.

divided. A finger is pushed up from behind the stomach through the lesser omentum; the vessels constituting the right gastro-epiploic artery and vein are isolated, clipped, and divided. The duodenum is clamped, divided, and buried. On lifting the stomach up and to the left a number of avascular bands tethering it to the pancreas are exposed and severed. The left gastric artery is tied high up on the lesser curvature; stripping of the vascular leash downwards brings into relief a number of vessels on the anterior and posterior walls that require ligation.

Anastomosis.—The anastomosis is shown diagrammatically in *Fig.* 166, C. Two Payr's clamps are placed across the stomach at the proposed site of section, the upper one including rather less than

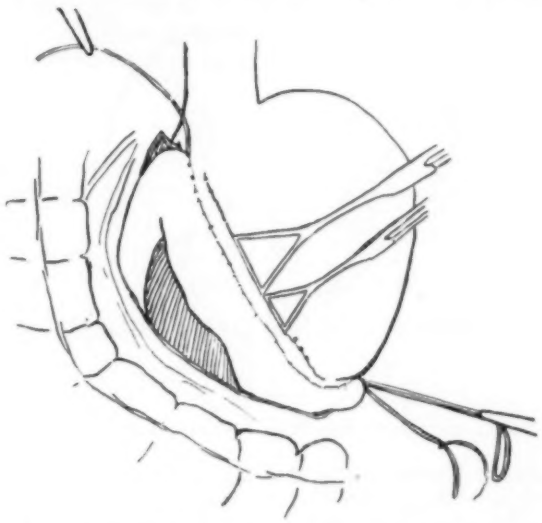

FIG. 171.—Both valves completed. Two Duval's tissue forceps lie on the gastric stoma; the combined width of the blades measures 3·8 cm.

one-third of the circumference (*Fig.* 167). The distal stomach is removed flush with the upper clamp, but a fringe is left to prevent the lower clamp

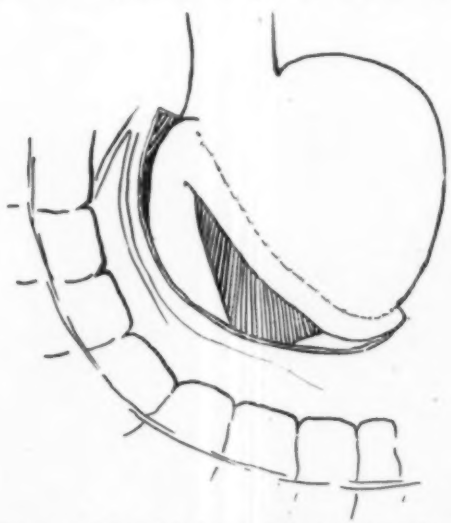

FIG. 173.—The original gastrojejunal seromuscular layer has been completed along the anterior wall of the stomach. It produces very effective burying of the corners.

from slipping. A continuous mattress suture of oo chromic catgut is inserted on the proximal side of the upper clamp, which is then removed; the same suture is retraced over the cut surface as a hæmostatic layer. The cut surface is then buried with a seromuscular layer of the same material, the upper end being retained as a stay suture (*Fig.* 168).

The next step is to make an opening in the mesocolon; before doing so, particularly in the case of a high resection, it is important to attend to two points—first, to assure that the opening be made at

the optimum place, the mesocolon should be lifted against the gastric remnant and the rent should be made in the part that lies most comfortably in that

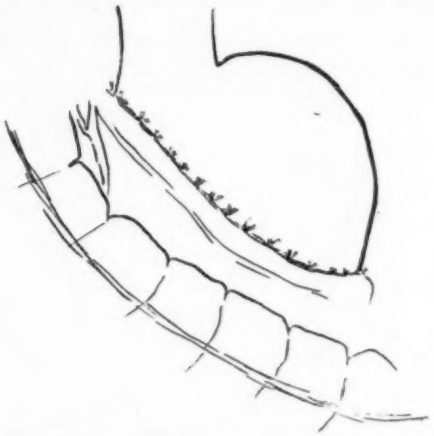

FIG. 174.—Closure of the rent in the mesocolon completed.

position; secondly, if the mesocolon is to lie comfortably around the gastric remnant it is essential that its division be not carried back more than about

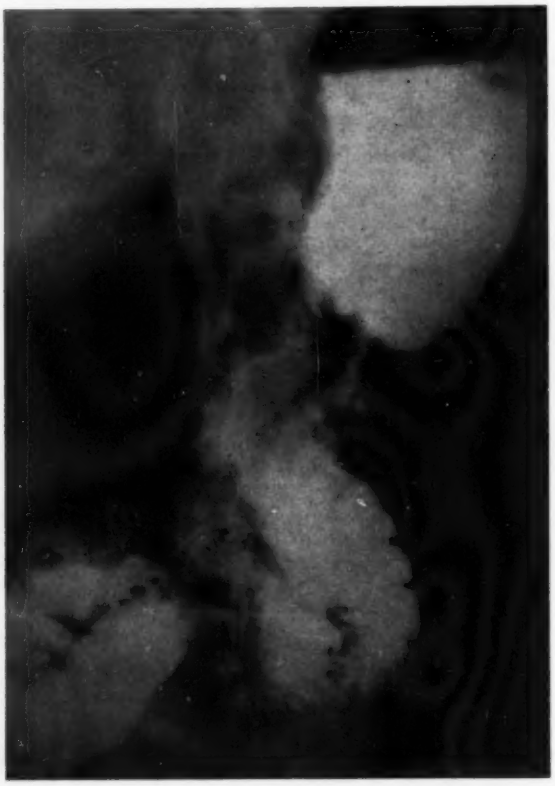

FIG. 175.—Double-valve resection; radiograph taken a few minutes after barium meal.

3·5 cm. from its root. This corner of the mesentery is then attached to the posterior wall of the stomach at the level of the tip of the Payr's clamp; in completing the suture of the mesocolon to the posterior gastric wall it follows that part of the right leaf will be attached to the upper third and part of the left leaf to the lower two-thirds (*Fig.* 169). The jejunum is sutured along the full length of the gastric cut surface, distal to the attachment of mesocolon, with oo chromic catgut (*Fig.* 170). The proximal loop is attached at the lesser curvature; its length is determined by finding the loop nearest the duodenojejunal flexure that lies comfortably in its new position.

The fringe left on the lower clamp is now excised and the clamp is removed; the edges do not gape, being now well sealed. A medium-sized and small Duval's tissue forceps are applied as in *Fig.* 171. The lower cut surface is closed in two layers.

The operation area is packed off; the jejunum is incised to a length corresponding with the central gastric stoma. In over 200 cases it has not been found necessary to tie any jejunal vessels; oozing from the left edge is negligible and the application of a large Duval forceps stops any oozing from the right. The gastric tissue forceps are removed and a sucker is inserted to aspirate any contents that have escaped the Ryle's tube. It is sometimes necessary to tie one or two vessels on the anterior wall of the stomach. The stoma, which measures about 3·8 cm., is closed with a hæmostatic layer of oo chromic catgut (*Fig.* 172), and the original seromuscular layer is completed to bury the whole cut surface (*Fig.* 173); in the completed anastomosis there is no corner that may leak.

The remainder of the mesocolic edge is sutured to the anterior gastric wall (*Fig.* 174).

FIG. 176.—Same case half an hour later; the gastric remnant is emptying gradually and there is even distribution in the small intestine.

In some 5 per cent of cases shortness of the mesocolon makes an antecolic anastomosis necessary; in these cases the proximal loop has been attached to the greater curvature. Post-operative distension has been found invariable after an antecolic anastomosis and very rarely after a posterior one.

From personal experience the writer considers that this type of anastomosis limits the frequency and severity of the functional symptoms that may follow partial gastrectomy with gastrojejunal link-up. Though the stomach is empty in from one-half to one hour, the actual emptying is a more gradual process (*Figs.* 175, 176), and a fairly even distribution is obtained in the small intestine.

I wish to record my thanks to Drs. McCormick, Whyte, and Byrne for the excellent anæsthetic facilities supplied; to the house surgeons and nurses of Sir Patrick Dun's Hospital for their help and co-operation; to Dr. McDonogh and his staff for the X-ray investigations; and to the physicians who referred the cases to me.

I am indebted to the Editor of the *British Medical Journal* for permission to use *Figs.* 166 and 172. My thanks are due to Mrs. Henry for the operation sketches.

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TEREBRANT RODENT ULCER WITH WIDESPREAD BLOOD-BORNE METASTASES

BY ALAN H. HUNT, LONDON

THE following case is presented to place on record the exceptionally wide dissemination of a rodent ulcer of the terebrant type.

CASE REPORT

The patient, a woman of 65, attended the Royal Cancer Hospital in November, 1947, with a large ulcerating mass spreading from the inner to the outer angle of the left eye (*Fig.* 177). It had started as a pimple at the inner canthus four years previously.

FIG. 177.—Original terebrant rodent ulcer: basosquamous carcinoma.

To remove this tumour it was necessary to sacrifice the left maxilla from the hard palate upwards and exenterate the orbit. Histologically it was basosquamous throughout.

The cavity settled well (*Fig.* 178); and three and six months later several pieces removed for biopsy from various parts of it failed to reveal any further trace of growth.

The following procedure was carried out in two stages to close over the unsightly defect with a double layer of skin. It is illustrated because these cavities are troublesome to close, and the accepted methods of raising pedicle flaps usually entail a procedure involving at least three stages and extending over two months or more. Younger patients are more willing and better enabled to tolerate this somewhat tedious programme; in the elderly, however, a reduction in both the number of operations necessary and the time taken over the whole process is of great value. In the present instance the operations were completed and all dressings had been removed within

FIG. 178.—The cavity after maxillary resection and exenteration of orbit.

twenty-four days of commencing the first stage. This consisted of cutting a pattern of the cavity in lead foil and raising skin to this pattern from the forehead with its base situated on the anterior branch of the superficial temporal artery (*Fig.* 179). This flap and the corresponding area of epicranium were covered with a dermatome graft, the two epithelial surfaces being kept apart by a sheet of tantalum foil. The flap was sutured back in place for two weeks to allow it to heal.

FIG. 179.—To show the forehead pedicle flap raised and lined with skin to close the defect; the donor area is also grafted.

FIG. 180.—Showing the condition seven weeks after commencing plastic repair.

The second stage of the repair consisted of swinging the flap down into position over the defect and suturing it in two layers to the margin of the cavity, having incised around that margin and the edge of the flap to obtain good approximation. The small remaining area on the donor site was covered by a Thiersch graft. The graft took extremely well (*Fig.* 180).

She was kept under careful supervision and remained well until May, 1950, when she was again admitted, complaining of pain in the left sternoclavicular joint and in the lumbosacral region of the spine. Biopsy of a sternoclavicular mass was done, and section revealed basosquamous carcinoma identical with the original tumour. Radiography of the lumbosacral spine showed advanced osteoporosis and secondary deposits in the lumbar vertebræ (*Fig.* 181).

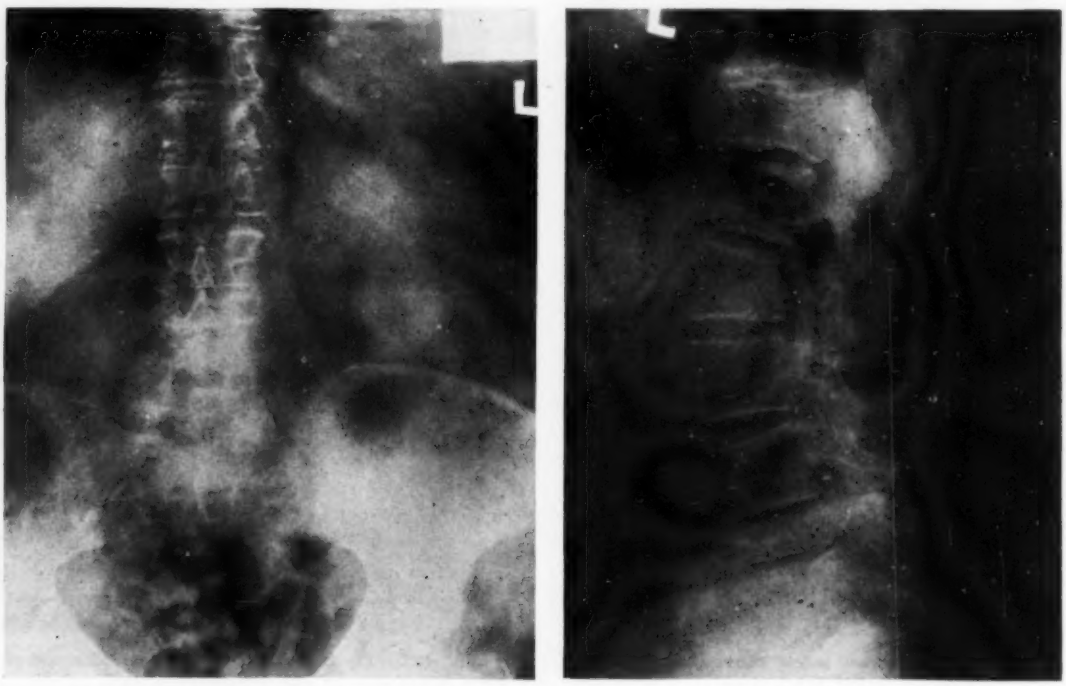

FIG. 181.—X-ray photographs showing diffuse spinal metastases with collapse of fourth lumbar vertebra.

Palliative X-ray therapy was given but the patient's condition deteriorated. A recurrence developed in the orbit, and she sustained a pathological fracture of the

left femur. Death occurred approximately seven years after the appearance of the first symptom and three years after the maxillary resection. There had never at any time been any sign of enlargement of the regional lymph-nodes.

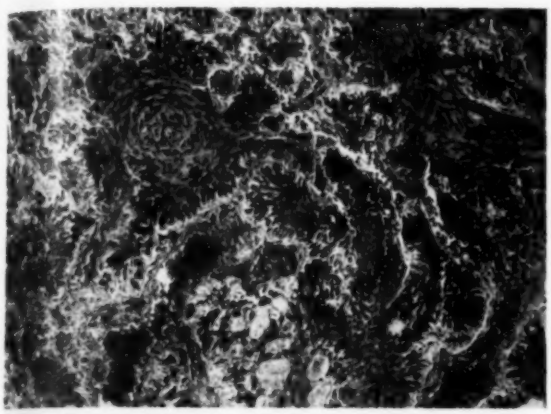

FIG. 182.—Metastatic basosquamous carcinoma in lung. (× 105.)

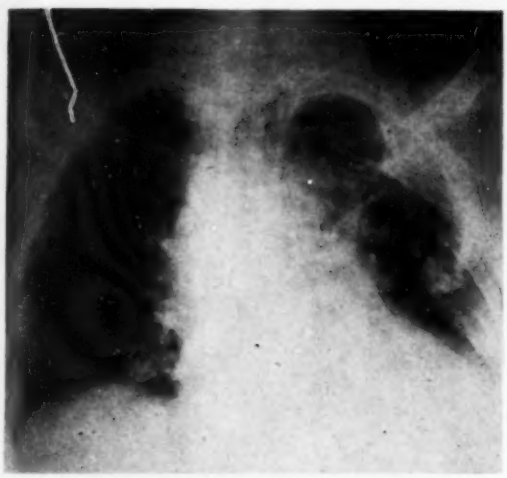

FIG. 183.—Radiograph of chest showing pulmonary metastases and porosis of clavicles and ribs.

At autopsy the presence of basosquamous carcinoma (*Fig.* 182) was confirmed in the following sites: in the recurrence below the lateral extremity of the left eyebrow; on the dura mater over the left anterior cranial fossa (where it did not invade the brain) and adjacent part of the sphenoid (where the left optic nerve was surrounded by growth); on the outer surface of the dura in the right parietal region; in areas of consolidation in the lung (*Fig.* 183); and in every bone examined—both clavicles, the left femur at the site of the fracture (*Fig.* 184), several ribs, the bodies of all thoracic and lumbar vertebræ,

FIG. 184.—Radiograph showing metastases in pubis and femur.

and both iliac crests. The pathologist confirmed that all the lymph-nodes, including the axillary, were free from metastases.

COMMENT

This blood-borne spread of a basosquamous carcinoma appears to be quite exceptional (Willis, 1934; de Nevasquez, 1941). It may have unavoidably occurred at the time of the resection.

I am most grateful to Professor R. A. Willis, Professor David Smithers, and Dr. J. W. Whittick for their co-operation, and to Miss J. Hunt for the photographs.

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SJÖGREN'S SYNDROME: A GENERAL DISEASE

By A. D. MORGAN and R. W. RAVEN, O.B.E., London

Sjögren described in 1933 a syndrome characterized by dry eyes (kerato-conjunctivitis sicca), dry mouth (xerostomia), recurrent parotid swellings, and polyarthritis, but the condition has received little attention in British medical literature. The ophthalmologist usually makes the diagnosis because the distressing ocular symptoms cause the patient to seek his advice. The non-ocular manifestations, however, may precede the others by several years and during this stage an erroneous diagnosis is often made.

The object of this paper is to call attention to the non-ocular aspects of the disease. Two cases are recorded of patients who presented with non-ocular symptoms. In each the parotid salivary gland was examined microscopically, and in one case the diagnosis was made by this means.

CASE REPORTS

Case 1.—A female, aged 56, complained of severe rheumatoid arthritis with gross deformities for thirteen years. She also suffered from chronic otitis media for four years. She was thin, with pale conjunctivæ (Hæmoglobin 74 per cent, R.B.C.s 4,130,000). No ocular symptoms were present, but she complained of a "dry throat" for two years.

A few weeks after admission, when she developed gingival ulcers, her mouth was re-examined. The lips were cracked at the corners, and the tongue, though moist, was bald and fissured. Four months after admission she developed a firm, tender swelling in the region of the right parotid salivary gland, which subsided slowly two weeks later. Within a month the left gland became swollen and she stated that she had had an "abscess" in the same region three years previously.

About this time she developed an angular conjunctivitis, with a sticky exudate, followed by left corneal ulceration. An E.S.R. showed a reading of 48 mm. for the first hour. Three months later the parotid swellings recurred, and subsided after a week.

The eye symptoms began to predominate, and she complained of constant soreness. The exudate became mucopurulent and yielded a growth of *Staph. aureus*. Finally she complained of loss of visual acuity, and reading became difficult. She now had photophobia and epiphora, and was found to have early right-sided corneal ulceration. About this time the condition was recognized for the first time as Sjögren's syndrome.

The following investigations were done:

Test-meal revealed achlorhydria. Glucose-tolerance test showed a rise to 225 mg. per cent after 1 hour, falling to 204 mg. per cent after 2 hours. There was no glycosuria. Radiography showed no salivary calculi.

She had a further attack of parotid swelling lasting two weeks, and shortly after she was transferred to another hospital after a stay of two years, during which her condition had slowly deteriorated. Five months later she died of cerebral embolism.

Autopsy revealed cerebral embolism, with evidence of recent thrombosis in the right auricular appendage of the heart, which also showed brown atrophy and healed rheumatic vegetations on the mitral valve. The lungs were emphysematous. The other viscera were normal. The parotid salivary gland was removed for microscopical examination.

Case 2.—An unmarried female, aged 67, was first seen on account of a left parotid swelling. Five years previously she had had an attack of what was called "mumps", which took the form of a tender, painful swelling in front of the left ear, not accompanied by fever. This subsided after two weeks, but never disappeared completely, and was liable to recur whenever she had a cold. The right parotid salivary gland was never affected.

Two years ago the swelling recurred for about six weeks, and she was referred to one of us (R. W. R.).

Fig. 185.—*Case* 2. Parotid swelling one year after operation.

On examination, she was under 7 st. in weight. There was entropion of both lower eyelids, especially the left, accompanied by blepharitis. In the left parotid region was a tender swelling involving the superior part of the gland and the socia parotidis. It was mobile, elastic, and had a smooth surface. Stensen's duct was normal, and pus could not be expressed from it.

The left parotid salivary gland was explored, and a portion was removed for histological examination. This showed atrophy of the epithelial elements and advanced round-cell infiltration, characteristic of the lesion in Sjögren's syndrome.

She was seen one year later and the following history was elicited. Since childhood she has complained bitterly of blue and cold extremities, with severe chilblains. She dislikes cold weather, and even in the hottest weather never perspires, her skin being always very dry. Twenty years ago, following a severe attack of influenza accompanied by a skin rash, she was given a diet excluding red meat and starchy foods. Since then she has scrupulously followed this diet, and suffers severe epigastric pain, or recurrence of the rash, if she fails to observe it. Appetite is poor, and slight constipation is present.

Five years ago she began to have attacks of "inflammation" in the eyes, photophobia, smarting pain, and a feeling of "a lot of gravel" in her eyes. During attacks the visual acuity is disturbed. She has not noticed absent lacrimation, and tears can be provoked by irritant odours, or by emotion. Four times in the last five years she has been treated for "ingrowing eyelashes", partial tarsectomy of the lower lids being ultimately carried out for the entropion.

For eighteen months she has had increasing dryness of the mouth, is always licking her lips, and has difficulty in satisfying her thirst. She occasionally has a sore mouth or tongue, but there is no dysphagia. The majority of her teeth are present, but in recent months a number have become carious.

She has mild arthritic swelling of the right carpus, but not elsewhere, and has frequent attacks of lumbar fibrositis. There is no history of menstrual irregularities, and the climacteric was over at the age of 50.

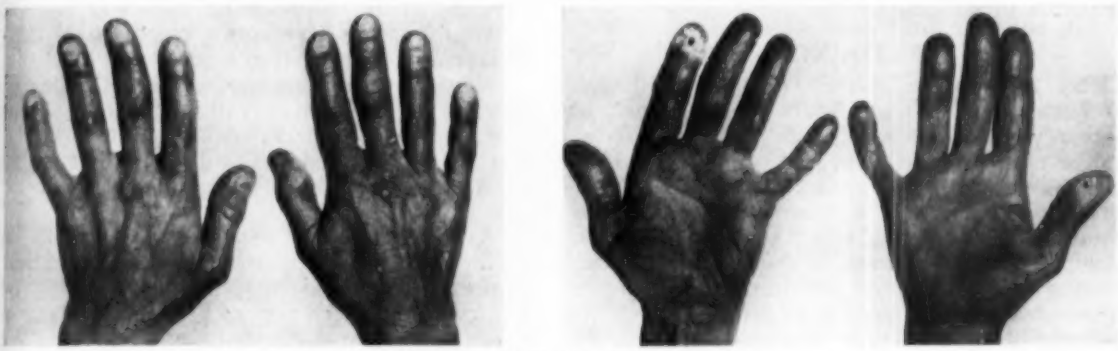

FIG. 186.—*Case* 2. Hands, showing chilblains.

On examination, the parotid swelling is 4 cm. in diameter, and the scar is well healed (*Fig.* 185). Both conjunctival sacs are inflamed, the lower tarsal conjunctiva having a bright red granular appearance. At the inner canthi is a whitish slimy exudate, but no filaments are seen with the naked eye. Trichiasis of the lower lids has been treated by partial tarsectomy. The fingers of both hands are covered with adhesive strips on account of an exacerbation of chilblains (*Fig.* 186).

OPHTHALMOLOGIST'S REPORT.—

"*Right eye*: *Rose-bengal* test shows slight stippling in the lower half of the cornea; *Schirmer test*, 3·5 mm. of moistening after 2½ minutes. *Left eye*: *Rose-bengal* test shows a triangular area of very intensive staining to the inner side of the cornea. The lower two-thirds of the cornea shows staining of similar intensity, with the presence of small tags, seen by the slit lamp, over the whole palpebral area; *Schirmer test*, 2 mm. of moistening after 2½ minutes. Diagnosis: Kerato-conjunctivitis sicca."

LABORATORY INVESTIGATIONS.—

Blood-count: Hæmoglobin 60 per cent (Haldane 8·28 g. per cent); R.B.C.s 3,500,000 per c.mm.; colour index 0·9; W.B.C.s 4,400 per c.mm. The blood-picture is that of a slightly desaturated normocytic anæmia.

Fasting blood-sugar 67 mg. per 100 c.c. Serum-calcium 11 mg. per 100 c.c. Fractional test-meal showed hypo-acidity, with the presence of free HCl.

HISTORICAL REVIEW

In 1888 W. B. Hadden presented at a meeting of the Clinical Society of London the case of a female, aged 65, who had complained of a dry mouth, dysphagia, diminished perspiration, and complete inability to lacrimate. Forty-five years afterwards Sjögren recognized that these peculiar features constituted a definite syndrome. This emphasizes its rarity, although during that period isolated cases were recorded which would probably be called Sjögren's syndrome to-day. Among these may be mentioned the cases of Fuchs (1919), Chamberlain (1930), Critchley and Meadows (1932), and in each instance the patient attended on account of parotid enlargement, the eye condition being secondary.

For fifty years before Sjögren's paper ophthalmologists were familiar with the condition of keratitis filamentosa, in which dryness of the eyes is accompanied by the presence of filaments on the cornea. Duke-Elder (1930) considers the essential feature is a deficiency of lacrimal secretion, and prefers the term 'keratitis sicca'. This lesion was generally regarded as of local origin until 1926, when Gougerot described 3 cases which showed, in addition to dryness of the conjunctivæ, progressive atrophy of the salivary glands and dryness of the nose, larynx, and vulva. The following year Mulock Houwer (1927) observed that 5 of a series of 10 cases of keratitis filamentosa were also suffering from chronic arthritis. In 1930 Duke-Elder drew attention to the fact that several cases of keratitis sicca had been accompanied by defective secretion of the salivary glands and dry skin in menopausal women.

In 1933 Sjögren showed conclusively that the ocular manifestations were only part of a general symptom-complex, and recorded 19 cases, all females, and mostly menopausal at the date of onset of symptoms. These included smarting of the eyes, photophobia, absence of lacrimation, and sometimes diminished visual acuity. Examination revealed hyperæmia of the conjunctivæ, with the presence of thready filaments attached to the cornea. Associated features, not always present, were dry mouth and nose, diminished salivation, early caries or falling out of the teeth, recurrent parotid swellings, absence of sweating, and polyarthritis.

Additional symptoms, less common, have been added since. They are anæmia, which might be hypochromic (Weber and Schluter, 1937) or of the P.A. type (Mulock Houwer, 1927; Grosz, 1936); lymphocytosis (Sjögren, 1936); achlorhydria (Lisch, 1937); achylia (Weber and Schluter, 1937; Bruce, 1941); acrocyanosis and Raynaud phenomena (Bruce, 1941; Belz, 1948); dysphagia (Garcia, 1947); aphonia; severe constipation (Espildora Luque, Mosser, and Gormaz, 1948, b). These subsidiary

features were reviewed by Parkes Weber (1945, b), who also added secondary cough, dryness and atrophy of the vulva, alopecia, raised E.S.R., low blood-pressure, hypo- or hyperglycæmia, and low serum-calcium. Beetham (1935) described a case with splenomegaly; Sheldon (1938) reported Sjögren's syndrome in association with sclerodermia and pigmentation of the legs.

Good accounts of series investigated are those of Sjögren, 19 (1933); Beetham, 9 (1935); Hamilton, 6 (1940); Bruce, 14 (1941); and Gifford, Puntenney, and Bellows, 12 (1943).

Since 1933 the disease has been universally associated with the name of Sjögren, except by Sjögren, who suggests (1940, a) that the term 'kerato-conjunctivitis sicca' be replaced by 'dacro-sialo-adenopathia atrophicans'.

INCIDENCE

Delay in recognizing the syndrome, although cases were recorded sporadically over a period of forty-five years, suggests that it is rare. Sjögren (1933) gave the figure of 1 in 2000 of his ophthalmological out-patients; Beetham (1935) 1 in 20,000 patients; and at the Wilmer Ophthalmological Institute, MacLean (1945) saw 7 cases in five years. In 1947, however, Stenstam, in a series of 495 cases presenting with rheumatoid arthritis, found evidence of kerato-conjunctivitis sicca in 47 (11 per cent). As rheumatoid arthritis is not a rare condition, he concluded that Sjögren's syndrome must be relatively common, a belief difficult to reconcile with the experience of others. Thus Sorsby (quoted by Weber, 1946) found kerato-conjunctivitis sicca a rare complication of rheumatoid arthritis. Holm (1949), using the rose-bengal test in 500 rheumatoid cases, found 9·4 per cent had fully developed kerato-conjunctivitis sicca, while a further 4·8 per cent showed partial development. His theories on the aetiology, pathology, diagnosis, and treatment have to be interpreted on this basis, and are therefore not applicable to Sjögren's syndrome as it is understood by other authors. It is probable that the last word has not been said on this subject.

AETIOLOGY

The paucity of knowledge on the aetiology of this curious condition may be gauged by the multiplicity of divergent theories. All authors are agreed, however, that the vast majority of cases occur in females. Thus, out of a total of 50 cases in the various series of Mulock Houwer (1927), Sjögren (1933), Beetham (1935), and Gifford and others (1943), only 3 were males.

Endocrine Theory.—Fuchs (1919) was the first to suggest that the condition was related to the menopause and may have an endocrine basis; this is still widely accepted. Most case reports show that the onset of symptoms coincides with the climacteric. Lisch (1937), however, pointed out that signs of parotid involvement might antedate the ocular symptoms by years, and that the association of the menopause with the appearance of eye symptoms might be coincidental. Espildora Luque and others (1948, b) quote several instances in females in their twenties and thirties in whom menstruation was perfectly normal. In one of these, parotid symptoms developed at the age of 11, five years before the onset of menstruation, and were followed by kerato-conjunctivitis sicca at 16, rapid dental caries at 21, and arthritis at 25.

The endocrine theory, however, rests on more than the age incidence. Krasso (1930) described kerato-conjunctivitis sicca following oöphorectomy, and MacLean (1945) recorded symptoms in a woman who had undergone pan-hysterectomy for suspected tuberculosis fourteen years earlier. Fried and Goldzieher (1944) claimed a virtual cure in a female aged 55 by the use of stilbœstrol, progynon B, and progesterone. Brückner (1945) observed remarkable improvement in a woman of 47 after a course of perandren linguetts (Ciba), with relapse when the treatment was suspended for a week. Friedman and Gernand (1946) found their case was relieved by stilbœstrol, while Hermann's cases (1948) did well on vitamin B_2 and testosterone.

None of the protagonists of the endocrine theory offer an explanation of the occasional incidence in males, apart from Fried and Goldzieher (1944), who remind us that males also produce œstrogens and may suffer from a hormone deficiency of this type.

Avitaminosis.—The main basis for this theory appears to be the experimental work of Yudkin and Lambert (1922), who, by feeding animals on vitamin-deficient diets, were able to produce changes in the cornea and lacrimal glands resembling those seen in Sjögren's syndrome. Lack of vitamins A, B_2, C, and PP have all been suggested (Clement, 1946). Chamberlain (1930) reported improvement, by balanced diet and vitamins, in a patient who all her life had lived on sugary and starchy foods. Grosz (1936) believed that the syndrome was the result of derangement of the hæmopoietic system due to avitaminosis. Franceschetti (1941) saw a resemblance to the Plummer-Vinson syndrome, and reported improvement of several cases on vitamin B_2. Lisch (1937), Gotfredson (1947), Drouet and Thomas (1948), and Holm (1949) found no evidence of vitamin deficiency, and in recent years vitamin therapy has been abandoned.

Chronic Infection.—The round-cell infiltration, progressing to atrophy and fibrosis of the lacrimal and salivary glands, is suggestive of a chronic inflammatory process. No pathogenic organisms have been isolated from the eyes or the salivary glands, except in the presence of secondary infection, such as corneal ulcer or parotid abscess. Beetham (1935) performed biopsies on enlarged lymph-nodes in the neck which histologically suggested chronic infection. The Dalsgaard-Nielsens (1937) and Stenstam (1947) believe that the parotid lesions are due to chronic infection, presumably of the ascending type, due to dryness of the mouth.

Grütter (1943) showed that there is a virus, normally in the mouth and nasopharynx, capable of producing changes like those of kerato-conjunctivitis sicca when introduced into the eyes of animals; and Garcia (1947) believes that infection by the virus is a factor in the production of corneal filaments. Espildora Luque and others (1948, b) found tonsillar infection a constant feature in their cases, and suggest an infective basis for the arthritis.

Neurotropic Factors.—Engelking (1928) was the first to describe keratitis filamentosa following Gasserian ganglionectomy. The Dalsgaard-Nielsens (1937), developing their infective theory, concluded that the syndrome was due to chronic infection of the vegetative nervous system. Weber (1945, a) also suggested a derangement of the vegetative nervous system, without specifying infection. Espildora Luque and others (1948, b) discuss the possibility of central nervous origin, and cite a case which followed electrical shock. In Critchley and Meadows' case (1932) symptoms appeared to follow mental shock. One of Coverdale's cases (1948) followed fracture of the skull, and Duke-Elder (1930) notes that Wagenmann in 1893 recorded a similar injury resulting in absence of lacrimation.

Other theories of causation are a hereditary factor (Lisch, 1937; Coverdale, 1948); rheumatic fever (Knapp, 1929); and adrenal insufficiency (Bassalino, 1936).

From the above it is clear that no single theory hitherto advanced is capable of explaining all the published cases. Holm (1949) believes that Sjögren's assumption that kerato-conjunctivitis is a disease *sui generis* is fundamentally wrong. He holds that it is firstly a local eye affection with manifold aetiologies, secondly a part phenomenon in known systemic illnesses, and finally a part phenomenon in a syndrome which has several aetiologies, known and unknown (e.g., hormonal, neurological, etc.). Weber and Schluter (1937) conclude that Sjögren's syndrome must be considered in the light of a group of diseases, including thyrotoxicosis, Hashimoto's disease, achlorhydric anæmia, and ulcerative colitis.

CLINICAL FEATURES

The most rational classification is that suggested by Hamilton (1947), who recognizes three groups :—

1. Those with a low result with the Schirmer test (*see below*) but no keratitis.
2. Those with a low result with the Schirmer test and showing keratitis.
3. Those with a low result with the Schirmer test and showing keratitis and other features of Sjögren's syndrome.

Ocular Manifestations.—The ocular features have been fully described by Sjögren (1933), with accounts in English by Beetham (1935), Bruce (1941), MacLean (1945), and Duke-Elder and Goldsmith (1951).

The patient complains of itching, smarting, a gritty sensation below the eyelids, photophobia, epiphora, and sometimes loss of visual acuity. She is often unable to lacrimate, although smarting is not invariably accompanied by dry eyes (MacLean, 1945).

The conjunctivæ are hyperæmic, with papillary hypertrophy and slimy whitish threads of exudate. Attached to the lower half of the cornea may be several short filaments 1–5 mm. in length. When these encroach on the centre of the cornea, loss of visual acuity may ensue. On the surface of the intervening cornea are minute defects, demonstrable by fluorescin. A watery solution of rose-bengal produces triangular areas, bands, or smaller patches on either side of the cornea, claimed by some observers to be pathognomonic of kerato-conjunctivitis sicca.

Lacrimal activity is characteristically reduced or absent, as shown by Schirmer's test (1903), which consists of inserting narrow strips of filter paper into the conjunctival sac and measuring the extent to which they are moistened. The symptoms are always bilateral, and the lacrimal glands are never tender or swollen, important points in the differential diagnosis.

The eye symptoms occur late in the syndrome, and may have been preceded for several years by dry mouth (Chamberlain, 1930; Critchley and Meadows, 1932; Lutman and Favata, 1946); by parotid swellings (Chamberlain, 1930; Espildora Luque and others, 1948, b); or by joint pains (Stenstam, 1947). If the non-ocular symptoms are severe, the patient may consult her doctor before the development of eye symptoms for a parotid swelling or arthritis, and it is in these cases that the diagnosis may be missed.

Non-ocular Manifestations.—It seems that the commonest non-ocular features are dry mouth, polyarthritis, and parotid swelling.

Dry Mouth (Xerostomia).—Depends more on diminished salivation than on the atrophic changes in the buccal mucosa. It is not commonly a presenting symptom, but is occasionally severe enough to cause difficulty in swallowing dry food. Though dry mouth may occur independently, the impression is gained that when it is accompanied by swelling of salivary glands, the degree of xerostomia is usually severe.

Parotid Swelling.—Though the submaxillary and sublingual salivary glands are sometimes involved, the parotids are most frequently affected. As a rule one side becomes swollen, followed by the other, the glands being firm and occasionally tender (Bruce, 1941). Regression without suppuration occurs in a week or so, but may last months and is sometimes permanent (MacLean, 1945). The swellings may be accompanied by fever, possibly caused by an intercurrent ascending infection from a dry mouth. The characteristic pathological changes may occur in the absence of swelling but are responsible for the dry mouth (Critchley and Meadows, 1932). It is also significant that the lacrimal glands, which show a similar pathological picture, are never enlarged. There are thus grounds for believing that the periodic swellings are secondary phenomena due to superadded infection. It is sometimes possible to express pus from the ducts of swollen glands (Chamberlain, 1930; Sjögren, 1933) and abscess formation has been reported (Weber, 1945, a; Allenic, 1947).

Arthritis.—There is polyarthritis of the rheumatoid type, which usually precedes the eye symptoms (Stenstam, 1947) and is often severe (Gifford and others, 1943). Mulock Houwer (1927) found the joints of the hands most frequently affected, otherwise there appears to be nothing distinctive about this symptom. The raised E.S.R. is presumably related to the joint condition.

Skin and Mucous Membranes.—Apart from the diminished secretion of the lacrimal and salivary glands, there is a general tendency to dryness of the skin and certain mucous membranes. Absence of perspiration is frequently noted, as well as dryness of the nose and mouth. The tongue may be atrophic

or cracked, while atrophy of the laryngeal and pharyngeal mucosa may be associated with dysphagia, secondary cough, and aphonia. Dryness of the vagina is reported by Weber (1945, b), Friedman and Gernand (1946), and Garcia (1947), while loss of hair is recorded by Weber (1945, b) and Mussio-Fournier and Poumeau-Delille (1946). Sclerodermia was observed in Sjögren's syndrome by Sheldon (1938).

Dental Changes.—In view of the age group it is not surprising that many patients are edentulous, but even in younger patients there is an unnatural history of dental caries, crumbling, or falling out of teeth, even though they are well cared for (Chamberlain, 1930). One patient of Espildora Luque and others (1948, b) lost all her teeth at the age of 21 in the course of two months. The relationship of dental changes to the absence of saliva is not clearly established.

Digestive Tract.—Espildora Luque and others (1948, b) found that mild digestive symptoms are common, and three of their cases showed hypoacidity. Achlorhydria was reported by Lisch (1937) and achylia by Weber and Schluter (1937). The relationship of these findings to blood changes has not been clearly established. One case (Espildora Luque and others, 1948, b), was so constipated that during the year she was under observation her bowels opened naturally on one occasion only.

Blood Changes.—Both microcytic hypochromic anæmia and anæmia of hyperchromic macrocytic type have been recorded (Weber, 1945, b; Grosz, 1936). Sjögren (1933) observed lymphocytosis in the absence of anæmia. Frequently the blood-count has been normal. Beetham (1935) observed three cases of lymphadenopathy and one of splenomegaly.

Vascular Disorders.—Acrocyanosis was recorded by Bruce (1941) and Raynaud phenomena by Belz (1948). Weber (1945, b) includes among secondary phenomena telangiectasia of the lips and finger-tips, and low blood-pressure.

Central Nervous System.—Weber (1945, b) mentions mental changes and epileptic fits among the rarer complications.

Blood Chemistry.—Hyperglycæmia and glycosuria were reported by Critchley and Meadows (1932); *low* blood-sugar and low blood-calcium by Weber (1945, b).

PATHOLOGY

Ocular Changes.—Sjögren (1933) found the *conjunctiva* swollen with œdema, with vesicle formation and shedding of the superficial layers, leaving a ragged surface, sometimes completely denuded of conjunctiva; or greatly thinned, with flattening of the cells and detachment of the superficial lamella. There is often a subepithelial round-cell infiltration, sometimes mingled with eosinophils.

These changes are not ascribed to dryness *per se*, but to metaplasia and hydropic degeneration of the conjunctiva in an attempt to provide its own secretion. The *corneal epithelium* is flattened, or thinned, and in places absent altogether, loose ends of tissue forming the characteristic filaments. The rest of the bulb is normal.

It is difficult to see why arrest of lacrimation should not cause these changes, since elsewhere Sjögren (1938, c) described a case of excision of the lacrimal gland followed by changes identical with those of kerato-conjunctivitis sicca. Moreover, the rapidity with which a number of cases have improved following surgical occlusion of the tear-ducts, thereby conserving the tears, suggests a direct relationship between lacrimal activity and kerato-conjunctivitis sicca.

Garcia (1947) alone believes that the corneal filaments result from rupture of vesicles caused by a virus.

Lacrimal Glands.—The pathology of the lacrimal glands was described by Albrich (1928) as a round-celled infiltration followed by atrophy and fibrous replacement of the parenchyma. Subsequent accounts (Beetham, 1935; Sjögren, 1938, b; Lutman and Favata, 1946) have not added materially to these findings. The process bears a close resemblance to the changes in the salivary glands.

Parotid Salivary Glands.—The lesions, once believed inflammatory, were described in detail by Sjögren (1938, a, b). The essential changes are epithelial atrophy, with replacement by large numbers of round cells, and ultimately fibrosis. In his final publication on the pathology of the syndrome (1940, b) Sjögren maintained that the earliest change is a granular degeneration of the cytoplasm of the secreting cells, which shrink until they resemble lymphocytes; and that true lymphocytic infiltration occurs only in the late fibrous stages of the disease. This opinion is not shared by some observers, including ouselves. Our findings are discussed later.

Sjögren emphasized that these changes occurred irrespective of swelling of the gland, in this respect differing from Mikulicz's syndrome, where the infiltration of lacrimal and salivary glands is responsible for their enlargement. Hamilton (1947) believes that many cases in the literature labelled Mikulicz's disease are really Sjögren's syndrome. He adds that Mikulicz's description of painless benign tumours of the lacrimal and salivary glands must be the criterion by which the diagnosis is made. It would appear from the literature that Mikulicz's syndrome has no pathological identity other than leukæmia, lymphosarcoma, and uveo-parotid fever. In Sjögren's syndrome, however, the salivary gland histology is distinctive and quite unlike that of leukæmia or lymphosarcoma (Sjögren, 1940, b). Thus a case regarded as Mikulicz's syndrome by Smith and Bump (1928) could, on the photomicrographs alone, be classed as Sjögren's syndrome.

Other Findings.—Similar changes have been observed in the sublingual and submaxillary salivary glands (Sjögren, 1933; Lutman and Favata, 1946). Focal round-cell infiltration of the labial mucosa (Sjögren, 1933), nasal mucosa (Sjögren, 1935), and the buccal mucosa (Espildora Luque and others, 1948, a), have all been recorded. Autopsies have failed to reveal significant lesions in the internal organs (Sjögren, 1933; Bruce, 1941).

The chemistry of the saliva, blood, urine, etc., have been extensively studied by Creyx and Levy (1948) and Drouet and Thomas (1948) without revealing data of great significance.

In examining the material at our disposal, two main impressions were gained:—

1. That the microscopical appearances of the cases are strikingly similar, and that this picture differs from any comparable lesion of the salivary glands.

The appearances in general conformed to those of the photomicrographs in articles by Sjögren and others. Disparity in the extent to which lobules are involved suggests a process spreading along the

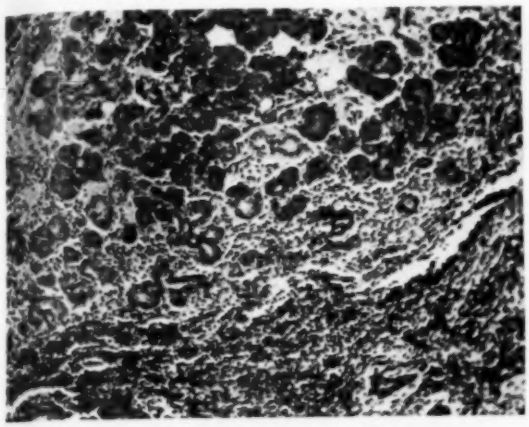

FIG. 187.—*Case* 2. Margin of surviving lobule. (Hæmatoxylin-eosin.) (× 84.)

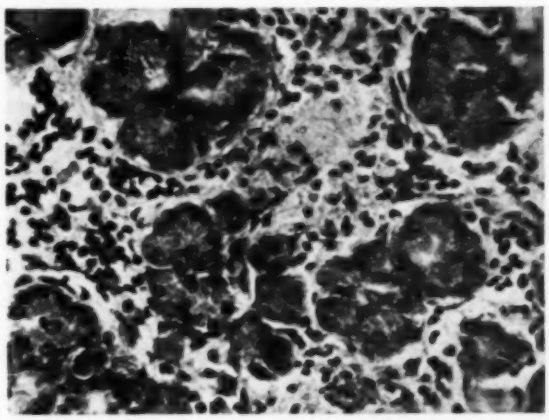

FIG. 188.—*Case* 2. Early lymphocytic infiltration of parenchyma. (Hæmatoxylin-eosin.) (× 285.)

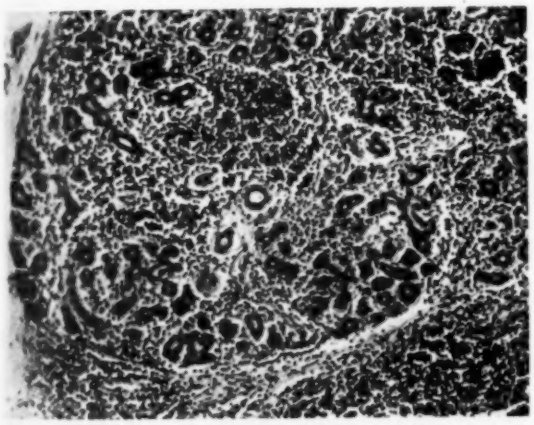

FIG. 189.—*Case* 1. Epithelial atrophy and lymphoid infiltration. (Hæmatoxylin-eosin.) (× 84.)

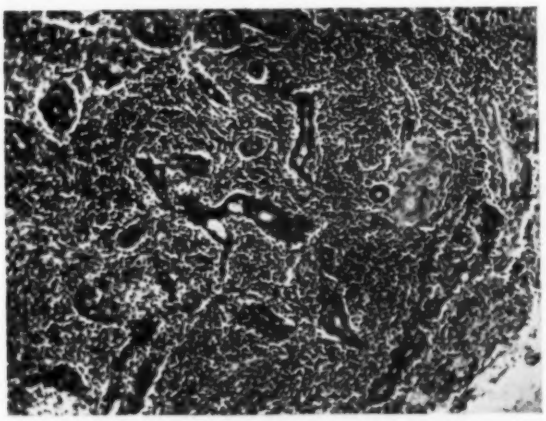

FIG. 190.—*Case* 2. Epithelial atrophy and lymphoid infiltration. (Hæmatoxylin-eosin.) (× 84.)

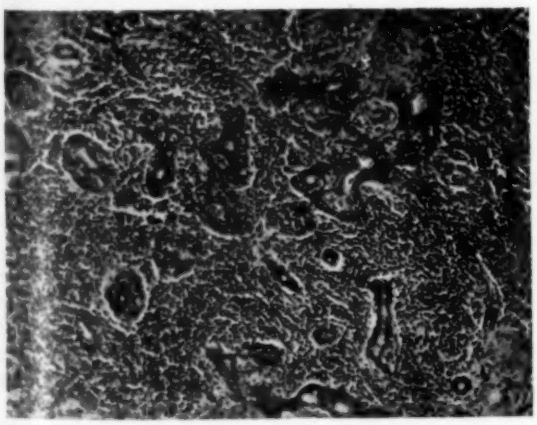

FIG. 191.—*Case* 2. Epithelial masses showing squamous metaplasia. (Hæmatoxylin-eosin.) (× 84.)

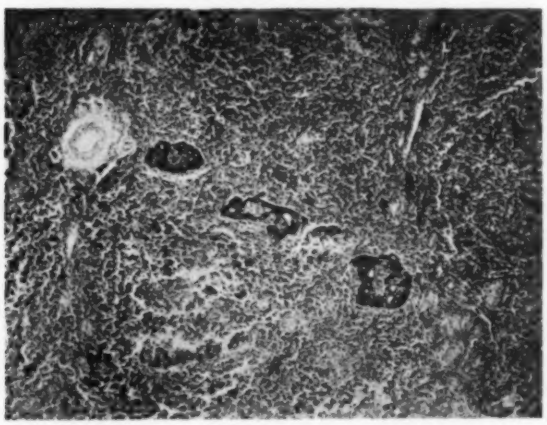

FIG. 192.—*Case* 1. Widely separated residual epithelial buds. (Hæmatoxylin-eosin.) (× 36.)

2. That the parotid involvement is uneven, whole lobules being almost completely spared, while those around them showed varying degrees of destruction (*Fig.* 187).

line of the ducts, e.g., by lymphatics, damaging some lobules and sparing others. This may explain the partial involvement of some parotids noted clinically. Assuming this hypothesis is correct, it

would be reasonable to infer that the varying degrees of lobular involvement roughly represent stages in the evolution of the lesion. If this is so, the sequence of events appears to be as follows :—

a. The earliest change is a true lymphocytic infiltration of the parenchyma before there is any significant evidence of cytoplasmic degeneration in the secreting cells (*Fig*. 188). In this respect our findings differ from those of Sjögren (*see above*).

b. As lymphoid infiltration becomes more marked, the secreting cells undergo atrophy, with shrinkage of cytoplasm, and become arranged in small duct-like structures, with a central lumen (*Figs*. 189, 190).

c. Lymphoid tissue later exceeds in amount the residual epithelium, which is arranged in isolated, irregularly-shaped masses showing a squamous metaplasia, staining more darkly around the periphery and containing several acinar spaces (*Fig*. 191). At this stage it may be difficult to distinguish individual atrophic epithelial cells from lymphocytes (Grignolo, 1945).

d. The epithelial masses degenerate into smaller rounded buds, some with one or two acinar spaces, many solid, and all widely separated by masses of lymphoid tissue (*Fig*. 192).

e. Finally only lymphoid tissue is seen, intersected by fibrous bands. Embedded in the lymphoid tissue there may be condensed and darkly-staining clumps, possibly representing the final stages of epithelial disintegration (*Fig*. 193).

The larger *ducts* are surrounded in some cases by a zone of lymphoid tissue (*Fig*. 194), in others by dense fibrosis. In the former, the lymphocytes may be seen apparently invading the lumen from without inwards, the lining epithelium being infiltrated with lymphocytes and showing hydropic degeneration (*Fig*. 195).

For purposes of comparison sections from a variety of infiltrative lesions of the parotid salivary gland were examined. None showed appearances comparable to stages *b*, *c*, and *d* of Sjögren's syndrome as described above. In acute *ascending infections* the ducts are distended by polymorphonuclear leucocytes, which later emigrate to form abscesses (*Fig*. 196).

In long-standing *obstruction* (salivary calculus) a progressive atrophy of epithelium occurs, with mild round-cell infiltration followed by fibrosis (*Fig*. 197), but the massive lymphoid infiltration and formation of epithelial buds seen in Sjögren's syndrome do not occur. The leukæmic forms of Mikulicz's syndrome show lymphocytic infiltration around the ducts,

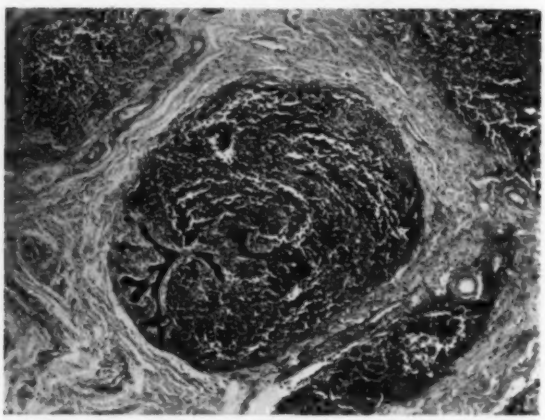

FIG. 193.—*Case* 1. Completely atrophic lobule with peripheral fibrosis. (Hæmatoxylin-eosin.) (× 36.)

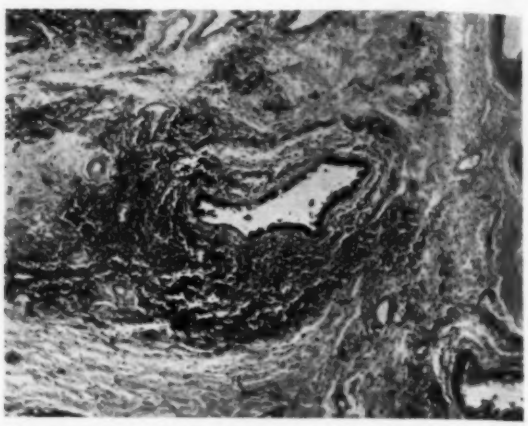

FIG. 194.—*Case* 1. Lymphocytic infiltration around ducts. (Hæmatoxylin-eosin.) (× 36.)

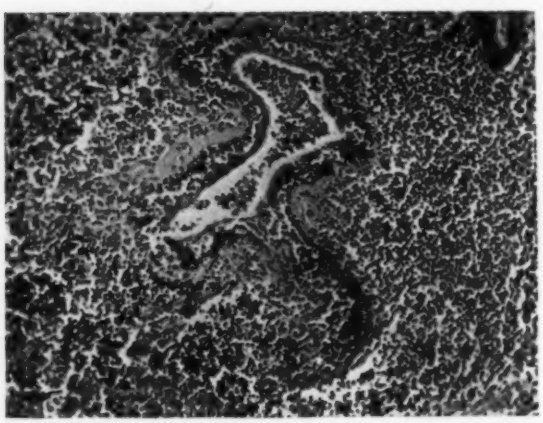

FIG. 195.—*Case* 1. Lymphocytes emigrating into lumen of duct. (Hæmatoxylin-eosin.) (× 84.)

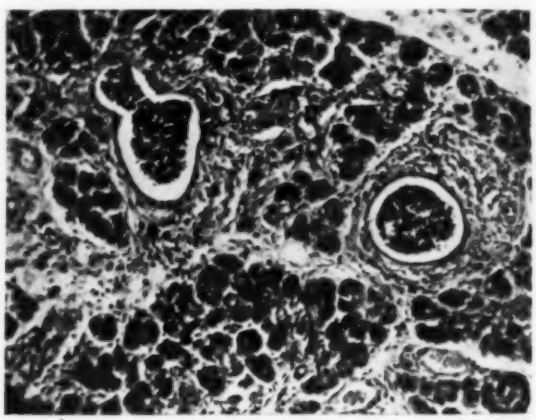

FIG. 196.—Acute ascending infection showing smaller ducts distended by pus. (Hæmatoxylin-eosin.) (× 84.)

spreading out into the parenchyma (*Fig.* 198). At a later stage the lobules become fragmented into groups of atrophic epithelial cells, widely separated by lymphocytes (*Fig.* 199), but the distortion found in Sjögren's syndrome is not observed.

Holm (1949) examined the parotids of 6 patients with kerato-conjunctivitis sicca, and failed to convince himself that the degree of lymphocytic infiltration was pathological, much less specific. From his illustrations the parotid lesions were not of the severity seen in our cases and those described and illustrated by Sjögren and many others. We are unable to accept his view that the lymphocytic infiltration seen in senile glands (*Fig.* 200) is in any way comparable with the changes of Sjögren's syndrome.

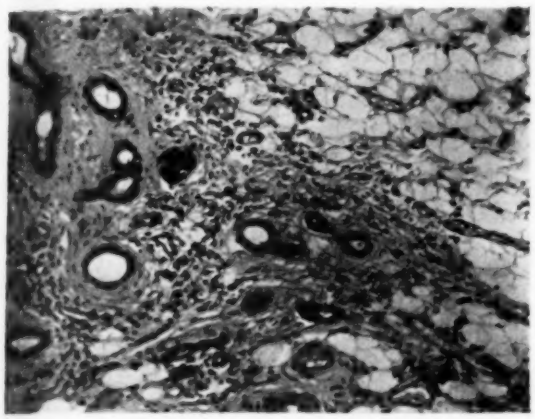

FIG. 197.—Atrophy in long-standing obstruction of Stensen's duct. (Hæmatoxylin-eosin.) (× 84.)

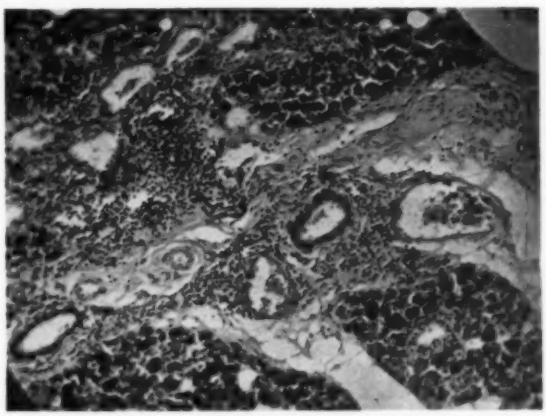

FIG. 198.—Early leukæmic infiltration (Mikulicz's syndrome). (Hæmatoxylin-eosin.) (× 72.)

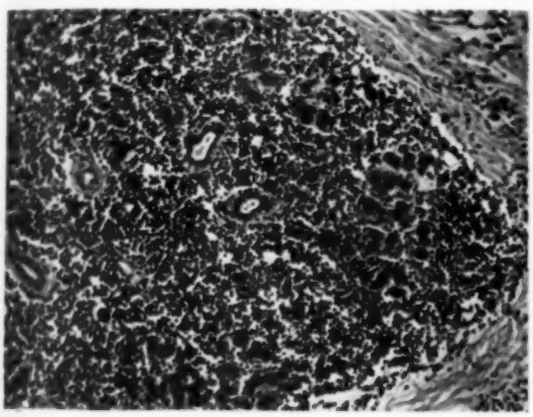

FIG. 199.—Mikulicz's syndrome in chronic lymphatic leukæmia. (Hæmatoxylin-eosin.) (× 84.)

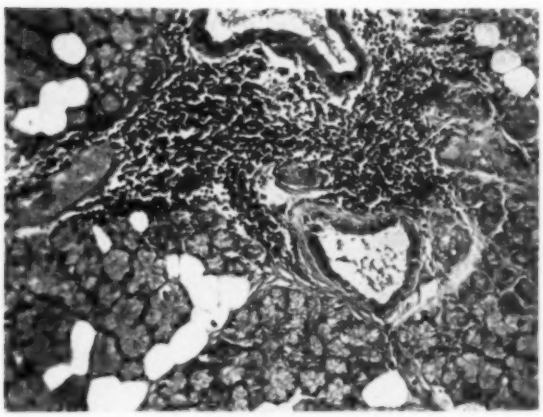

FIG. 200.—Senile changes in parotid. (Hæmatoxylin-eosin.) (× 84.)

DIAGNOSIS

To the ophthalmologist the patient with eye symptoms presents no great diagnostic problem, especially when the patient has other features of the syndrome. The only condition likely to be mistaken for kerato-conjunctivitis sicca is xerophthalmia due to avitaminosis, which can be eliminated by the therapeutic test.

Sjögren considered the rose-bengal test diagnostic of kerato-conjunctivitis sicca; however, Holm (1949), on the basis of this test, found that 14·2 per cent of his rheumatoid cases gave a positive result, even though many had normal lacrimation. This appears to us to set limits on the value of this test as a diagnostic agent.

It is the patients who present before the onset of eye symptoms that are liable to remain undiagnosed.

The differential diagnosis of salivary gland swelling has been detailed by Bruce (1941) and may be summarized as follows :—

DISEASE	DIFFERENTIATING FEATURES
Mumps	Typical history
Salivary calculus	Typical history. Radiograph may reveal calculus
Mikulicz's syndrome	Swelling of lacrimal glands. Changes in blood and bone-marrow
Uveo-parotid fever	Lacrimation normal. Tendency to iritis
Sarcoidosis	Skin lesions. Negative tuberculin test. Kveim test may be positive
Parinaud's conjunctivitis	Typical history. Lacrimation normal
Tularæmia	Typical history. Culture of organism. Specific agglutinations

Bruce adds " benign lymphoma ", but this is a purely pathological diagnosis and should be made only when aleukæmic leukæmia and Sjögren's syndrome have been excluded. In our opinion a biopsy of the parotid gland may be of considerable assistance. Judging by our own experience and from photomicrographs in the literature, the fully developed lesion is sufficiently characteristic to be considered pathognomonic. Punch biopsy is not recommended in view of the small amount of material obtained, and the danger of damaging the facial nerve. Development of a salivary fistula following biopsy, though warned against by some authors, is not recorded in the literature of Sjögren's syndrome and is not our experience.

TREATMENT

Vitamin therapy has been abandoned, and success from hormone therapy is claimed only in isolated instances (Fried and Goldzieher, 1944; Brückner, 1945; Friedman and Gernand, 1946; Hermann, 1948). As dramatic improvement was said to follow, it seems worth while to give hormones a trial. Pending the discovery of a specific cure, however, the non-ocular manifestations must be treated symptomatically. For dry mouth, Espildora Luque and others (1948, b) recommended pilocarpine and potassium iodide.

The kerato-conjunctivitis sicca has been treated surgically by occluding the tear-ducts and thereby conserving the tears. This method was first reported by Beetham (1935), who destroyed the canaliculi by electrocoagulation. Gifford and others (1943) preferred stitching them, while Espildora Luque and others (1948, b) used the thermocautery. In several instances relief of symptoms and partial reversal of the ocular lesions followed in a striking manner.

For conservative treatment Sjögren used artificial tears applied with a dropper. MacLean (1945) employed an artificial tear dropper fitted to a spectacle frame.

SUMMARY

1. Two cases of Sjögren's syndrome presenting with non-ocular manifestations are reported.

2. The aetiology and symptomatolology are discussed and the literature is reviewed.

3. The severity of ocular lesions has stimulated the interest of ophthalmologists for many years. As ocular manifestations may be delayed, wider recognition of the syndrome by the profession is desirable.

4. The microscopical changes in the parotid glands are compared with those of other lesions. It is stressed that the changes in Sjögren's syndrome are highly characteristic.

5. Biopsy of the gland may be of assistance in diagnosing doubtful cases.

We are indebted to Mr. Frederick Ridley and Dr. Louis Minski, of the Belmont Hospital, Sutton, for clinical data relating to *Case* 1 and to Dr. Ifor Williams for pathological material; to Mr. P. D. Trevor-Roper, Westminster Hospital, for the ophthalmological report of *Case* 2, and to the Medical Photography Department of Westminster Hospital for the clinical photographs.

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EXPERIMENTAL SURGERY

INFLUENCE OF ANTICOAGULANT ADMINISTRATION ON THE RATE OF RECANALIZATION OF EXPERIMENTALLY THROMBOSED VEINS

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THOUGH the value of dicoumarin and its derivatives in the treatment of venous thrombosis is now fully established, the rationale of its administration in cases where the already formed thrombus is no longer propagating is uncertain. Anticoagulants are usually given after the presence of a thrombus has been diagnosed clinically, even though the clot may have been in situ for a variable period before detection. The anticoagulant drugs are recognized to interfere with the clotting mechanism and thus to prevent any further spread of the thrombus, and it is in virtue of this action that heparin and dicoumarin have been advocated. In a preliminary communication (Kubik and Wright, 1950), however, we suggested that anticoagulant drugs, provided they depress the prothrombin level of the blood satisfactorily, may also influence, directly or indirectly, the rate of recanalization of veins experimentally thrombosed, even though administration is started after occlusion of the vessel is complete. The present paper sets out in greater detail further observations on this aspect of anticoagulant therapy.

METHOD

To evaluate the effect of anticoagulant treatment on the rate of recanalization of veins occluded by experimentally produced thrombi, it was necessary to be able to induce *standard* lengths of blood-clot. The following technique proved satisfactory in rabbits. After careful shaving, a specially constructed clip was placed on the margin of the ear (*Fig.* 201). This clip consisted of hinged plastic arms in which rubber reservoirs from fountain-pens were affixed. These rubber lips replaced the band of a sphygmomanometer and could be inflated to any desired pressure without causing mechanical damage to the surrounding tissues. Venous occlusion was complete at 40 mm. Hg, and thrombosis was induced in the length of marginal vein enclosed in the curve of the clip by the injection either of sodium morrhuate (5 per cent) or of thrombin solution (1000 units/c.c.). The injected substance was retained in the vein for 10 minutes before release of the clip's pressure.

After thrombosis had been induced, the rabbits were placed in one of two groups. *Group* 1 received 300 mg./kilo body-weight of 'Tromexan' (bis-3-3'-(4-oxycoumarinyl) ethyl acetate)* by stomach tube daily, starting 24–48 hours after thrombosing and when the first phlebogram has been taken. Tromexan is not soluble in neutral solution, but a satisfactorily stable suspension may be obtained by grinding the active substance with methyl ethyl cellulose* (4 per cent) in water. *Group* 2 were kept as controls with no treatment. Since one ear only was thrombosed in the first instance, some animals after complete recanalization of this vein, while included in one group, were later transferred to the other group and the opposite ear vein was then thrombosed. At least one month elapsed between the time that the first vein became patent before such animals were included in the other group. The effect of any treatment given during the first part of the experiment had, therefore, passed off by the time they were transferred. We feel that these animals which appear in both groups constitute a most useful series for the assessment of the effects of the anticoagulant treatment.

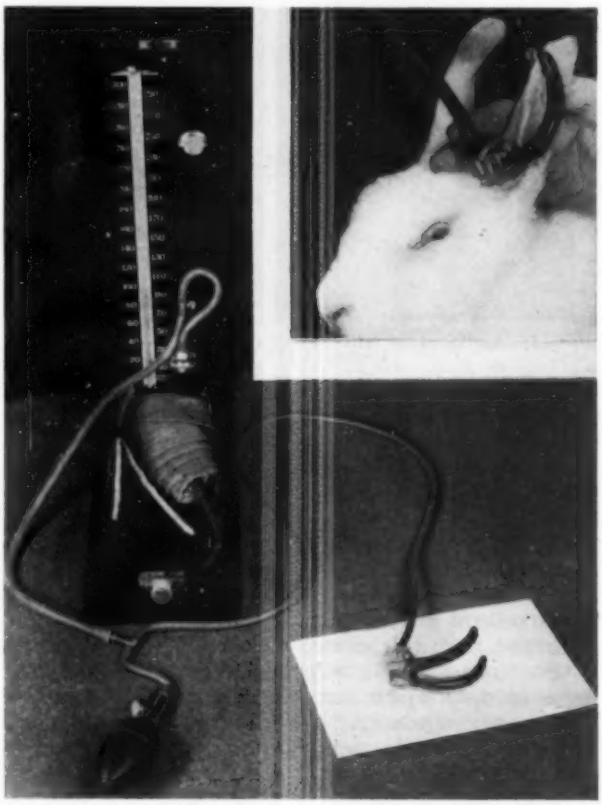

FIG. 201.—Apparatus used in the production of *standard* thrombi. Inset: Clip in position.

The patency of the ear veins was studied by phlebography, using 0·5 c.c. 50 per cent diodone as contrast medium and exposure factors of 53 kv.,

* Supplied by courtesy of Pharmaceutical Laboratories, Geigy, Ltd.

* 'Cellofas A', Imperial Chemical Industries, Ltd.

50 ma., 0·1 sec., and a focus-film distance of 80 cm. 'Improved Fast Ilfex Film', double wrapped, was used throughout. To ensure that the animals remained quiet during the exposure, light anæsthesia was induced by the intravenous injection of 0·75 c.c./kilo body-weight of veterinary nembutal. The first radiograph was taken within 24 hours of

FIG. 202.—Phlebograms showing recanalization of ear veins. Thrombosis was induced 24 hours prior to first radiograph in both instances.

thrombosing to demonstrate that the vein was fully occluded, and the subsequent progress of recanalization was followed at weekly intervals, using the same technique. Extreme care must be exercised in making the diodone injections, since even the smallest leakage causes necrosis of the surrounding tissues and sloughing of the ear margin. In our series several rabbits from both groups had to be discarded from this cause.

For the sake of comparison and to ensure that those animals which received Tromexan responded to the anticoagulant, prothrombin-time estimations by Quick's single-stage method were frequently made in the course of the experiments on blood samples from animals in both groups.

Since it was possible that Tromexan might have a direct effect upon fibrinolytic activity, plasmas from rabbits of both groups were examined to detect any such change by the method of Macfarlane and Biggs (1946). Dilutions of $\frac{1}{16}$, $\frac{1}{32}$, and $\frac{1}{64}$ were set up for each plasma and the degree of digestion of the fibrin clot was inspected at the end of 24 hours' incubation. Prothrombin-time measurements were in all instances made upon the same plasma samples that were used for the fibrinolytic tests.

RESULTS

The times taken for the experimentally produced *standard* thrombi in the ear veins of rabbits to undergo recanalization are set out in *Table I*. It can be seen that the average time for the group of treated animals is 3·0 ± 0·21 weeks, while that for the controls is almost three times as long. Though the total numbers in each group are not large, the difference (5·1) between them is statistically significant, being nearly four times its standard error (1·3).

Fig. 202 shows the radiographs from both ears of rabbit No. 30. The right ear was thrombosed and the animal was treated and included in group 1. This ear was patent in 3 weeks. Later, in the control group, the left ear was thrombosed in the same manner. After 16 weeks there was practically no change from the initial condition. These radiographs are typical of those obtained throughout the series, but this animal and also No. 35 are the most

Table I.—TIME TAKEN (WEEKS) FOR THE RECANALIZATION OF THROMBOSED EAR VEINS

RABBIT NO.	WEEKS ELAPSING BEFORE RECANALIZATION	
	GROUP 1 (Treated)	Group 2 (Untreated)
	Morrnuate induced thrombi	
4	3	
10	2	
11		3
12	3	
14	4	
18		4
21		8
22		6
23		5
30	3	16+
	Thrombin induced thrombi	
32	2	4
33	2	6
35	3	16+
36	3	12
41	4	
42	4	8
44	4	
45	4	9
Average	3·0 ± 0·21	8·1 ± 1·28

striking examples since the *control* side never became patent.

The prothrombin-time estimations of plasma from animals in the two groups were markedly different and showed that the response to Tromexan was satisfactory. The average times for the two groups were 32·6 ± 3·17 sec. and 9·5 ± 0·26 sec. respectively.

The plasma fibrinolytic activity tests were performed on the same blood samples as were used for prothrombin-time measurements. No digestion of the fibrin clot was ever detected in any of the tubes after 24 hours incubation, and no difference was observed between plasmas from animals from the two groups.

DISCUSSION

In the foregoing experiments an attempt was made to imitate, as far as possible, the formation of clinically occurring thrombi. Those produced by sodium morrhuate were initiated by damage to the intima, which is followed by the deposition of platelets from the flowing blood to from white plaques on which mixed thrombus subsequently forms. The thrombin-produced clots, on the other hand, represent the red coagulum which occurs with propagated thrombosis where local damage to the blood-vessels is minimal. Copley and Stefko (1947) had a similar intention when they attempted to simulate the processes of thrombophlebitis and phlebothrombosis by methods not unlike ours. In our series of animals, all those up to and including No. 30 were thrombosed by the morrhuate method, while the rest received thrombin. It is evident from the results, shown in *Table I*, that the rate of recanalization of both these types of thrombus is similar and they have not, therefore, been separated in this discussion.

As far as we are aware, very little is known about the recanalization of already thrombosed vessels in the presence of anticoagulant. That clot may disappear rapidly clinicians have few reasons to doubt, but the mechanism by which it is accomplished has not yet been studied. It is known that, in the post-operative period, after the small vessels of the surgical site have become plugged by thrombus and hæmorrhage is completely arrested, the administration even many days later of anticoagulants may, within a short time, cause some degree of bleeding from the wound. Such bleeding usually only occurs if the prothrombin activity of the blood is allowed to fall below 20 per cent of normality. It is, moreover, confined to the wound site, a fact which is of interest in the light of the present findings. We have noticed repeatedly that hæmorrhage frequently occurs in rats which have had their tail-tips cut for blood-sampling several days prior to the first dose of Tromexan; in untreated rats, however, this never occurs. It appears that in these cases, both in rats and in man, the thrombus plugs are 'dissolved' or 'washed away' so that the vessel is again patent and bleeding can take place.

Rabinowich and Pines (1949) have shown that heparin could "cause the solution or disappearance of a thrombus already formed if injected in sufficient quantities in the early stages of clot formation". Their work confirms earlier observations (Rowntree and Shionoya, 1927; Best, Cambell, and Maclean, 1938; Solandt and Best, 1940) that heparin prevents the formation of massive white thrombi though small aggregations of platelets may form and break up again. Platelet adhesiveness is decreased in the presence of both heparin and dicoumarol (Wright, 1941, 1945; Spooner and Meyer, 1944), and this accounts, in part, for the dispersal of recently formed thrombi. None of these authors, however, discuss the progress of thrombi formed some time before the administration of the anticoagulant.

Recently Enria and Ferrero (1951) followed for 30 days the fate of thrombosed femoral veins in dogs. They induced thrombosis by partial clamping of the vessel, followed by damage to the intima by excoriation with a needle. The animals were divided into six groups, one of which received Tromexan daily. They studied, by phlebographic means, the development of the collateral circulation up to 30 days. From some of the dogs they removed the thrombosed portion of the vein for histological examination. Those from the Tromexan-treated group showed evidence of organization and recanalization, while the control group was still completely occluded. It must be stressed that the amounts of Tromexan given by them was small on a body-weight basis when compared with ours. Moreover, these authors did not carry out any prothrombin-time determinations to establish that the animals were responding satisfactorily to the drug.

It has been shown by Kunitz and Northrop (1936) that heparin has a lytic effect upon blood-clot, probably brought about by the inactivation of *plasmin* in the blood. From our observations it seems unlikely that Tromexan has any direct proteolytic action upon formed fibrin. The failure to digest fibrin clots, at any dilution of plasma, suggests that the balance between the enzyme *plasmin* and its inhibitor, *antiplasmin*, is not disturbed even though the prothrombin level of the blood is considerably reduced.

As a working hypothesis, the surface of a thrombus in contact with flowing blood may be supposed to undergo accretion through the continual deposition of fibrin film on its exposed surface. Any proteolytic action of the blood-enzymes is, therefore, apparently without effect. Where the clotting mechanism is impaired, however, as after the administration of anticoagulants, no such deposition can take place and the enzymic digestion of the fibrin network proceeds uninterruptedly. The action of the anticoagulant may, therefore, be an indirect one, which thus allows the recanalization of the vessel to take place in a shorter time than would occur under normal conditions.

SUMMARY

1. A method is described for producing *standard* sized thrombi in marginal ear veins of rabbits.

2. The rate of recanalization of such thrombi has been shown to be about three times as long in control animals as in those treated with Tromexan.

3. A possible explanation of this finding is put forward.

We wish to express our thanks to Dr. C. J. Hodson and members of the X-ray Diagnostic Department for their willing co-operation in this work; also to Mr. S. E. R. Mable, of the Physics Department, for constructing the special ear clip.

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A HISTOLOGICAL EXPLANATION FOR THE BENEFICIAL ACTION OF ENDOCRINE THERAPY IN CARCINOMA OF THE PROSTATE

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INTRODUCTION

ENDOCRINE therapy by the administration of œstrogens, or by orchidectomy, or a combination of both, is known to have a definite and valuable place in the treatment of carcinoma of the prostate. The idea of such therapy emerged after a considerable amount of experimental work had helped to determine the endocrine control of prostatic function, and had provided evidence about the possible cause of benign prostate hypertrophy. Some of this experimental work was carried out on dogs, the only mammals other than man known to suffer commonly from enlargement of the prostate. In 1935 De Jongh and Kok showed that œstrogens cause metaplasia of the prostatic acini of the dog prostate, and shortly afterwards Zuckerman and Groome (1937) and Zuckerman and McKeown (1938) noted that the changes due to œstrogenic stimulation are identical with those that occur spontaneously in certain enlarged prostates of dogs associated with carcinoma of the testis. These changes were the opposite of those induced by androgens, by which it could be supposed that they would be prevented.

Huggins and Clark (1940) showed that the administration of androgens to dogs stimulates the growth of the prostate and the secretion of prostatic fluid, and that these effects could be reversed by the administration of œstrogens. In 1941 Huggins, Stevens, and Hodges began to treat 21 cases of advanced carcinoma of the prostate by castration. Huggins (1946) published a report of these cases after five years, and stated that 4 were still alive and showed no sign of malignancy, 1 had a slowly growing tumour, but was otherwise in good health, and of the remainder 15 had obtained some benefit lasting from about three months to five years. Further, Huggins and Hodges (1941) reported that while androgens activated the tumour and initiated a sharp rise in the serum acid phosphatase value, œstrogens or castration produced an inhibitory effect with a corresponding fall in acid phosphatase.

Fergusson (1948) states that taking a general view of the symptomatic response of prostatic cancer to œstrogens, it seems that about 80 per cent of the cases show initial improvement which is sustained in 50 per cent for over a year. His histological follow-up by biopsies in patients showing clinical improvement indicated regressive changes in the neoplasm, and he states that neoplasms showing predominantly adenocarcinomatous structure tend to become more scirrhous in type, with considerable reduction of the quantity of malignant tissue in standard microscopical fields. Colston and Brendler (1947) stress the value of orchidectomy and œstrogen therapy in advanced inoperable carcinoma of the prostate and in reducing the size of moderately advanced tumours and so rendering them accessible to surgery. Dodds (1948), McCaffery and Hess (1948), Heckel (1948), and many others express similar views.

Although it is known that the beneficial action of œstrogen treatment is accompanied by fibrosis in the prostate (Fergusson and Pagel, 1945; Fergusson, 1946, 1948), no definite explanation has yet been found which explains the manner in which the response of the affected tissue is brought about (Dodds, 1948). It is unlikely to be due to any mitotic poisoning action on the cells as suggested by the work of Lettre (1943), who showed that mitosis in chicken-heart fibroblasts is inhibited by diethyl-stilbœstrol and believed that stilbœstrol had the same kind of mitotic poisoning action as colchicine. Ludford and Dmochowski (1947), by investigating the action of diethyl-stilbœstrol on ten different transplantable mouse tumours in mice of four inbred strains, were convinced that there was no justification to include stilbœstrol in the same class of mitotic poisons as colchicine and sodium cacodylate. They found that on these cancerous tumours stilbœstrol showed no specific inhibition of growth, and such inhibition as took place with relatively high doses was the result of a non-specific toxic action of stilbœstrol accompanied by a considerable loss of weight. Moreover, in tissue-culture experiments no indication was obtained of a specific action on the cancer cells, and no mitotic action was seen comparable to that of colchicine or its active derivatives. So, neither *in vivo* nor *in vitro* did stilbœstrol prove to have a mitotic poisoning action on the malignant cells.

The role played by the reticulo-endothelial system in the defence against cancer in general has been referred to by many workers. Stern (1941) showed that the function of the reticulo-endothelial

system as tested by the congo-red method was impaired in 86 per cent of patients with malignant disease. Brunschwig, Schmitz, and Clarke (1940) have shown by intravital staining that selective localization of Evans blue occurred in and around malignant tumours of varying types in a majority of human subjects, but that benign neoplasms did not show localization of the dye. Kavetzki and Diadjuscha (1937) showed that stimulation of the reticulo-endothelial system lowers the incidence of development of cancer metastases in rabbits inoculated intravenously with Brown-Pearce carcinoma, and that blockade of the system raises the incidence of tumour growth. These experiments suggest that stimulation of the reticulo-endothelial system may prevent metastases in human cancer. Diadjuscha (1937) has also shown that implantation of Ehrlich carcinoma into mouse liver or spleen and Flexner-Jobling carcinoma into rat testes was invariably successful when the reticulo-endothelial system was blocked, and rarely so when it was stimulated.

Since fibrosis always accompanies the beneficial action of œstrogen and castration treatment for carcinoma of the prostate, and the reticulo-endothelial system plays an important role in the defence against cancer, and since the genetic relations between reticulo-endothelial cells and fibroblasts are well known (Jaffe, 1938 ; Maximow and Bloom, 1945), it appeared desirable to study the effect of œstrogens on the reticulo-endothelial system and to ascertain whether or not the reticulo-endothelial cells take part in the development of the prostatic fibrosis.

MATERIAL AND METHODS

The present paper is based on the results of experiments carried out on 167 guinea-pigs which were divided into groups of intact males and orchidectomized and ovariectomized animals. One month at least was allowed to elapse after double orchidectomy and double ovariectomy to ensure complete recovery from the operation and the disappearance of testicular or ovarian hormones from the blood. All the animals received one daily subcutaneous injection of trypan blue at 4 p.m. for six days and were killed by chloroform the following day. The dosage of the dye was calculated on the basis of 0·8 ml. of a 1 per cent solution in distilled water per 100 g. body-weight. Six intact males and 10 orchidectomized and eighteen ovariectomized animals were given the dye only and were used as controls. The remainder were divided into groups which received one of the œstrogenic preparations daily at 10 a.m. for durations varying from six to twenty-eight days, during the last six days of which they also received the injections of dye.

All the females used were sexually mature virgins, proved by the vaginal smear method (Stockard and Papanicolaou, 1917) to have a regular cycle of sixteen days. They were divided into groups of nine, one group being double ovariectomized on the 4th day of the cycle and the other groups on the 8th, 12th, and 15th days. The date of killing of each female was arranged to correspond, had the ovaries been present, with the day of the cycle when the animal was double ovariectomized.

The œstrogens used were œstradiol benzoate, œstrone, stilbœstrol, stilbœstrol dipropionate, D.B.E. (αα di (*p*–ethoxyphenyl)–β–phenyl-bromo-ethylene), and dienœstrol. The œstrogen was given to a small number of animals by mouth, but usually by intramuscular injection. The daily dose varied from 0·1 mg. to 5 mg. Because of the low toxicity of œstradiol benzoate (Nicol and Helmy, 1951), œstradiol benzoate in a daily dose of 0·5 mg. intramuscularly was used for all the experiments in which œstrogenic treatment continued for more than six days.

Specimens were taken from the spleen, liver, lymph-nodes, bone marrow, skin and subcutaneous tissues, adrenal glands, and from the prostate or the uterine horns. After fixation in Heidenhain's 'Susa' fluid, sections were cut at 10 μ thick and stained with dilute carbol-fuchsine or weak eosin. The activity of the reticulo-endothelial system in the organs studied was measured by the number of dye-bearing cells and the intensity of the vital staining.

RESULTS

In all the groups of animals studied œstrogenic hormones produced hyperplasia and stimulation of the macrophages in the spleen, liver, lymph-nodes, prostate, or uterine horns and to a less extent in the bone-marrow and subcutaneous tissues. In the adrenal glands the cortex was hypertrophied, but no significant change was observed in the small number of vitally stained cells normally present.

In the spleen of intact male animals not given œstrogen (control animals) a relatively small number of the cells in the sinuses and the reticulum showed vital staining (*Fig.* 203). After injections of 0·5 mg. œstradiol benzoate daily for one week, dye-bearing cells, similar in appearance to those found in the control animals, appeared in both the splenic sinuses and the reticulum in slightly increased numbers (*Fig.* 204). The vitally stained cells are large, rounded, or oval, with an oval or kidney-shaped nucleus situated near the periphery of the cell. The dye granules vary in size, are coarse, and may completely mask the nucleus. When the daily injections of œstradiol benzoate were continued for three or four weeks the number of dye-bearing cells progressively increased, especially in the splenic sinuses, but also in the reticulum (*Figs.* 205, 206). The white pulp (Malpighian corpuscles) remained pale owing to the absence of vitally stained macrophages.

In marked contrast to the above appearances, the splenic sinuses in the orchidectomized animals not given hormone were dilated and contained many dye-bearing cells, and the general structure of the spleen looked more open (*Fig.* 207). The splenic reticulum, however, contained only a few dye-bearing cells. After injections of 0·5 mg. œstradiol benzoate daily for one, two, or three weeks the number of dye-bearing cells progressively increased both in the sinuses and recticulum, and the general structure of the spleen looked more normal (*Fig.* 208). When, however, the œstrogenic treatment was continued for four weeks, the splenic sinuses were dilated and contained in some animals numerous dye-bearing cells, in others a moderate number, and in others the sinuses were practically empty (*Fig.* 209), although

in the same animals the splenic vein, the intrahepatic branches of the portal vein, and the intralobular veins contained many dye-bearing cells (*Fig.* 210). The appearances, therefore, suggest that œstrogenic dye-bearing Kupffer cells were seen in the sections of the liver in the intact males not given hormone. After œstrogenic treatment, however, the number of vitally stained cells progressively increased and many

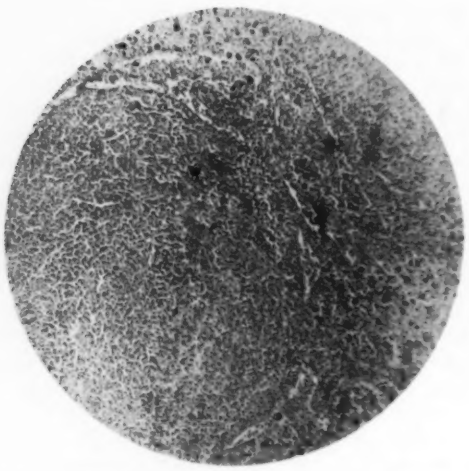

FIG. 203.—Photomicrograph of section of spleen of intact male control guinea-pig which received one subcutaneous injection of trypan blue daily for six days and was killed the following day. Shows a relatively small number of vitally stained cells in the sinuses and reticulum. The vitally stained cells appear black in the photomicrograph. (Weak eosin.) (× 150.)

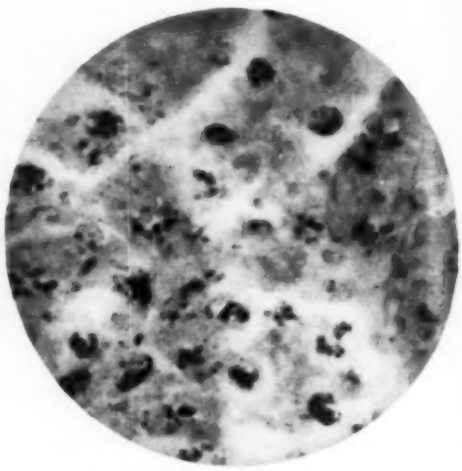

FIG. 204.—Photomicrograph of section of spleen of intact male guinea-pig which received 0·5 mg. œstradiol benzoate intramuscularly daily at 10 a.m. for one week, plus one subcutaneous injection of trypan blue daily at 4 p.m. during the last six days before being killed. Shows vitally stained cells in the sinuses and in the reticulum. The dye granules appear black in the photomicrograph. (Weak eosin.) (× 450.)

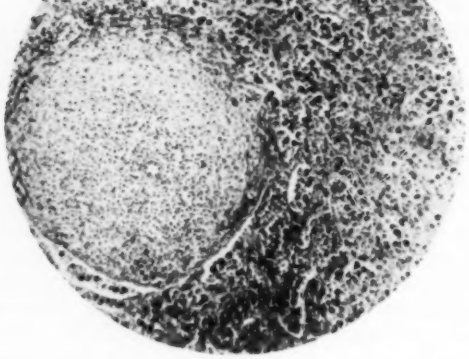

FIG. 205.—Photomicrograph of section of spleen of intact male guinea-pig which received 0·5 mg. œstradiol benzoate intramuscularly daily at 10 a.m. for four weeks, plus one subcutaneous injection of trypan blue daily at 4 p.m. during the last six days before being killed. Shows numerous vitally stained cells in the dilated sinuses of the red pulp and in the reticulum. The vitally stained cells appear black in the photomicrograph. (Weak eosin.) (× 150.)

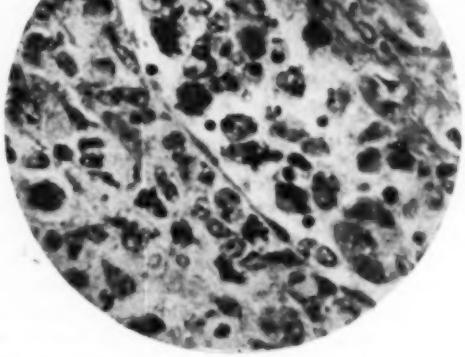

FIG. 206.—High-power view of section shown in *Fig.* 205. Shows numerous vitally stained cells in a splenic sinus and in the reticulum. No dye granules are present in the lymphocytes. (Carbol-fuchsine.) (× 450.)

treatment, especially when combined with orchidectomy, assists mobilization of the reticulo-endothelial cells from the spleen into the circulation.

In the liver, the reticulo-endothelial system is represented by the specialized phagocytic cells of Kupffer. Although in vitally stained animals the hepatic cells also contain fine dye granules, the Kupffer cells can be distinguished easily by their spindle-shaped or stellate appearance and by the coarse dye granules in the cytoplasm, which may be very numerous and mask the nucleus. Only a few cells were liberated and could be seen free in the tributaries of the hepatic veins. The increase in number of the dye-bearing cells and their mobilization as a result of the injections of œstradiol benzoate was still more marked in the orchidectomized animals.

In the lymph-nodes the same pattern of reaction was produced by œstrogen. The number of dye-bearing cells, particularly in the sinuses of the medulla, progressively increased and the response was more intense in the hormone-treated orchidectomized animals. The vitally stained cells in the lymph-nodes also belong to the group of reticulo-endothelial macrophages, and their concentration was always found to be greater in the medullary than in the

cortical sinuses. They are similar in appearance to the vitally stained cells found in the spleen and are three or four times larger than the small lymphocytes. No vital staining was noted in the lymphocytes.

FIG. 207.—Photomicrograph of section of spleen of orchidectomized guinea-pig which received one subcutaneous injection of trypan blue daily for six days and was killed on the following day. Shows dilated sinuses containing many vitally stained cells which appear black in the photomicrograph. A few vitally stained cells are present in the reticulum. (Weak eosin.) (× 150.)

FIG. 209.—Photomicrograph of section of spleen of orchidectomized guinea-pig which received 0·5 mg. œstradiol benzoate intramuscularly daily at 10 a.m. for four weeks, plus one subcutaneous injection of trypan blue daily at 4 p.m. during the last six days before being killed. Only a few vitally stained cells are present in the reticulum. The sinuses are dilated and empty of cells. The splenic vein in this animal contained numerous vitally stained cells. (Weak eosin.) (× 150.)

The prostate in the intact animals not given hormone contained only a few dye-bearing cells in the loose areolar tissue between the acini, which were surrounded only by a thin fibrous layer (*Fig.* 211). After œstrogenic treatment, the dye-bearing macrophages progressively increased in number and the layer of fibrous tissue around the acini increased in thickness, especially in the animals which received injections of hormone for three or four weeks (*Fig.* 212). Orchidectomy by itself seems to have a similar effect on the prostate, for in the orchidectomized animals not given hormone both the number of macrophages and the degree of fibrosis were greater than in the intact controls. With œstrogen treatment prostatic fibrosis in the orchidectomized animals was

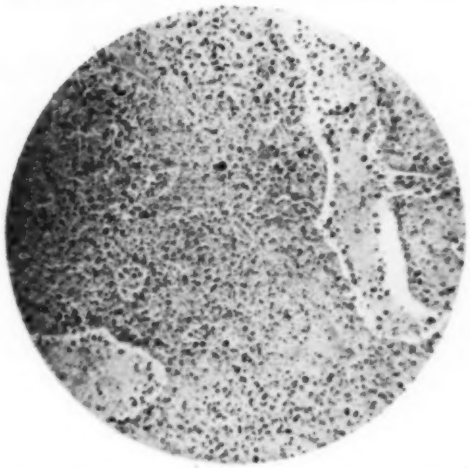

FIG. 208.—Photomicrograph of section of spleen of orchidectomized guinea-pig which received 0·5 mg. œstradiol benzoate intramuscularly daily at 10 a.m. for three weeks, plus one subcutaneous injection of trypan blue daily at 4 p.m. during the last six days before being killed. Shows numerous vitally stained cells in the sinuses and in the reticulum. The vitally stained cells appear black in the photomicrograph. (Weak eosin.) (× 150.)

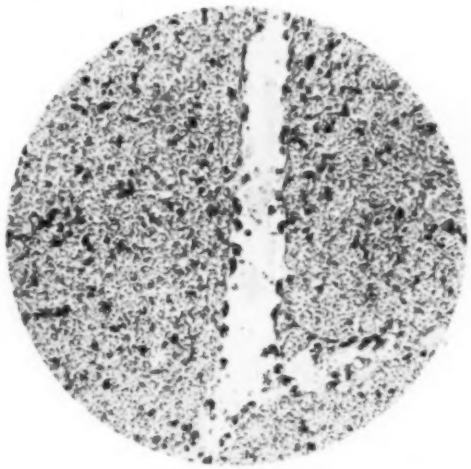

FIG. 210.—Photomicrograph of section of liver of orchidectomized guinea-pig which received 0·5 mg. œstradiol benzoate intramuscularly daily at 10 a.m. for four weeks, plus one subcutaneous injection of trypan blue daily at 4 p.m. during the last six days before being killed. Shows numerous vitally stained Kupffer cells in the liver lobules and many free dye-bearing cells in a hepatic vein. The vitally stained cells appear black in the photomicrograph. (Weak eosin.) (× 150.)

accelerated until, after injections of œstradiol benzoate for four weeks, the spaces between the acini were practically obliterated by dense fibrous tissue (*Fig.* 213). The acini were collapsed and the lining epithelium was thrown into folds. The histological picture suggests that the macrophages become transformed into fibroblasts and then into fibrous tissue around the acini. *Fig.* 214 shows the transition of the loose areolar tissue containing vitally stained globular macrophages with coarse dye granules into a layer of fusiform fibroblasts containing

fine dye granules, and finally into a concentric lamellated layer of dense fibrous tissue around the acini.

In the female animals the reticulo-endothelial system was also activated by œstrogens. Stimulation

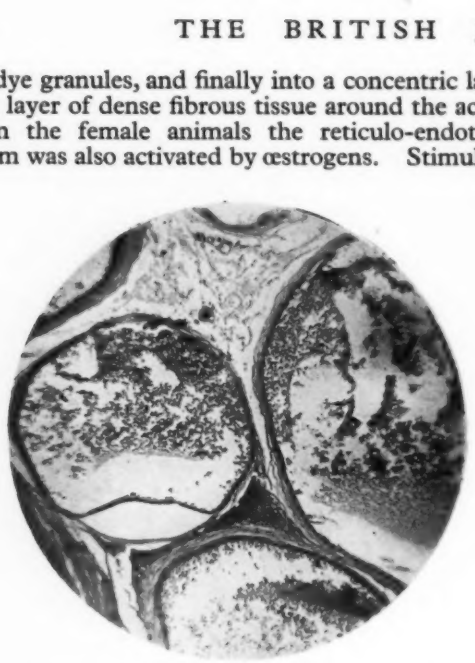

FIG. 211.—Photomicrograph of section of prostate of intact control guinea-pig which received one subcutaneous injection of trypan blue daily for six days and was killed the following day. The acini are surrounded by a thin fibrous layer and few vitally stained cells are present in the areolar tissue between them. (Weak eosin.) (× 150.)

FIG. 213.—Photomicrograph of section of prostate of orchidectomized guinea-pig which received 0·5 mg. œstradiol benzoate intramuscularly daily at 10 a.m. for four weeks, plus one subcutaneous injection of trypan blue daily at 4 p.m. during the last six days before being killed. The spaces between the acini are practically obliterated by dense fibrous tissue. The acini are collapsed and the lining epithelium thrown into folds. (Mallory.) (× 150.)

of the macrophages in the spleen, liver, and lymph-nodes, and mobilization of the cells into the circulation occurred as in the males. An intensified reaction could be obtained by giving a large daily dose of œstrogen (up to 5 mg.) for six days instead of a small daily dose (0·5 mg.) for four weeks.

Œstrogens also appeared to act on the secondary sex organs in the female in a manner comparable to their effect on the prostate in the males. In the uterine endometrium of the ovariectomized animals not given hormone, a moderate number of dye-bearing cells appeared only at a time, corresponding to what would have been the middle of the œstrous cycle had the ovaries been present. These vitally stained cells became greatly increased in number after

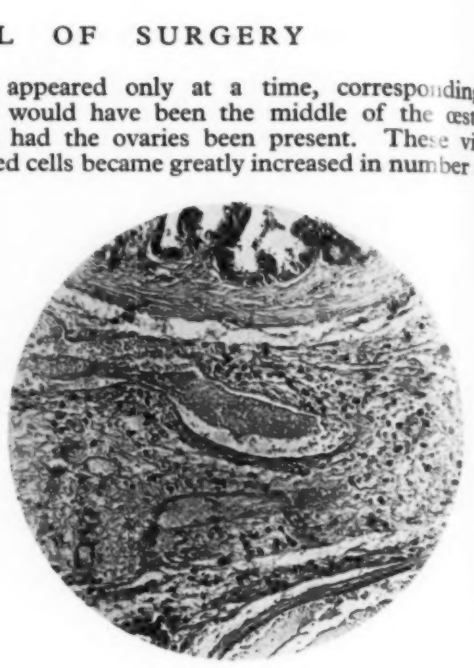

FIG. 212.—Photomicrograph of section of prostate of intact guinea-pig which received 0·5 mg. œstradiol benzoate intramuscularly daily at 10 a.m. for four weeks, plus one subcutaneous injection of trypan blue daily at 4 p.m. during the last six days before being killed. The acini are surrounded by a thickened fibrous layer and many vitally stained cells are present in the areolar tissue between them. The vitally stained cells appear black in the photomicrograph (Carbol-fuchsine.) (× 150.)

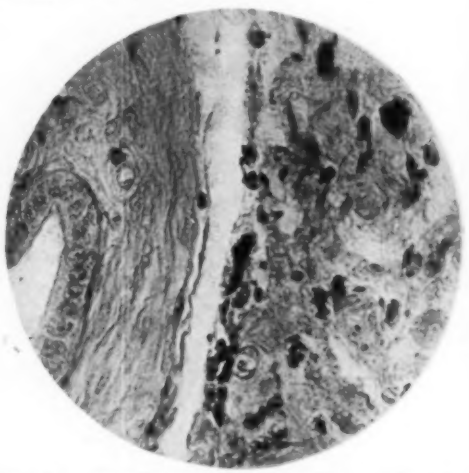

FIG. 214.—Photomicrograph of section of prostate of orchidectomized guinea-pig which received 0·5 mg. œstradiol benzoate intramuscularly daily at 10 a.m. for four weeks, plus one subcutaneous injection of trypan blue daily at 4 p.m. during the last six days before being killed. Shows a prostatic vesicle lined by cuboidal epithelium and surrounded by a dense fibrous layer. Outside this is young connective tissue with spindle-shaped dye-bearing cells and farther out large globular vitally stained macrophages are present in the areolar tissue. The dye granules appear black in the photomicrograph. (Weak eosin.) (× 450.)

a daily injection of 0·5 mg. œstradiol benzoate intramuscularly for seven days, but the maximum deposition remained about what would have been the middle of the œstrous cycle had the ovaries been present (*Fig.* 215). When the hormone treatment was continued for fourteen days marked hypertrophy of the endometrium resulted in increased cellularity of the stroma, the number of dye-bearing macrophages was greatly diminished, and the cyclic

concentration of vitally stained cells in relation to what would have been the phases of the œstrous cycle had the ovaries been left in situ disappeared.

Although all the œstrogens used had a stimulating effect on the reticulo-endothelial system, their potency in this respect varied from one preparation to the other. It was found in experiments on ovariectomized animals that with a daily dose of 0·1 mg.

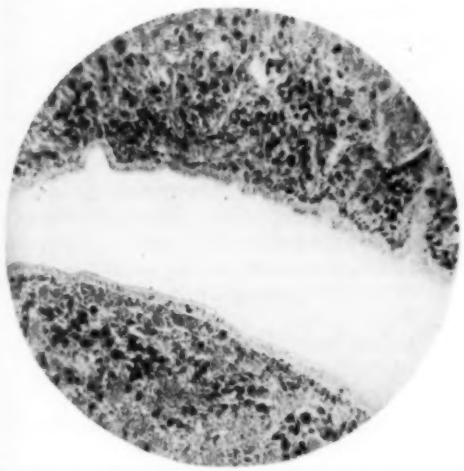

FIG. 215.—Photomicrograph of section of uterine horn of ovariectomized guinea-pig which received 0·5 mg. œstradiol benzoate intramuscularly daily at 10 a.m. for one week, plus one subcutaneous injection of trypan blue daily at 4 p.m. during the last six days before being killed on what would have been the eighth day of the œstrous cycle had the ovaries been present. The stratum compactum of the endometrium shows numerous vitally stained cells which appear black in the photomicrograph. (Weak eosin.) (× 150.)

for six days the descending order of activity of the various hormones was stilbœstrol dipropionate intramuscularly, œstradiol benzoate intramuscularly, œstrone intramuscularly, and dienœstrol by mouth. With a large daily dose of 5 mg. stilbœstrol dipropionate intramuscularly for six days or 5 mg. dienœstrol by mouth for three days, followed by 5 mg. stilbœstrol by mouth for three days, the macrophages in the spleen, liver, and lymph-nodes became reduced, while those in the uterine horns were increased in number. Moderate stimulation was obtained in the spleen, liver, lymph-nodes, and uterine horns after treatment for six days with a daily dose of 0·5–1 mg. œstradiol benzoate, 1–2 mg. D.B.E., 3 mg. dienœstrol, and 5 mg. stilbœstrol dipropionate. In the uterine horns the most intense results were produced by 5 mg. dienœstrol daily for three days, followed by 5 mg. stilbœstrol dipropionate daily for three days, whereas only very weak results were produced by 0·1 mg. dienœstrol for six days.

DISCUSSION

The findings in the above experiments in both the male and female animals indicate that œstrogens possess a strong stimulating influence on the reticulo-endothelial system which results in the appearance of large numbers of macrophages in the spleen, liver, and lymph-nodes, and in the mobilization of these macrophages into the circulation. The reticulo-endothelial system is apparently intimately related to the secondary sex organs, since it was found that together with the liberation of the cells from the reticulo-endothelial organs many macrophages appeared in the uterine horns in the female and in the prostate in the male. The relationship between the reticulo-endothelial system and the secondary sex organs has been demonstrated by Nicol (1935), who found that macrophages appear cyclically in the endometrium of the uterine horns of guinea-pigs and are greater in number in the follicular phase of the œstrous cycle. In the present research it was found that the cyclic behaviour of the macrophages still exists after ovariectomy and is intensified by moderate œstrogenic stimulation. This cyclic behaviour in ovariectomized animals may be due to an indirect pituitary control through an extra-ovarian œstrogen, possibly suprarenal, since the pituitary is known to possess an inherent cyclic activity (Smith and Engle, 1929; Wolfe, 1931; Wolfe, Cleveland, and Campbell, 1932; Cleveland and Wolfe, 1933).

Maintenance of the œstrogenic stimulation in the female animals was found to lead to an increased cellularity and hypertrophy of the endometrium, together with diminution in the number of the phagocytic cells. Other workers have recorded that œstrogenic treatment for longer periods of up to four months leads to fibrosis and even uterine and extragenital fibrous tumours (Lipschutz and Iglesias, 1938). The appearance in the endometrium of macrophages, which are known to be genetically related to fibroblasts (Jaffe, 1938; Maximow and Bloom, 1945) would seem, therefore, to be the first step in fibrosis. Their diminished number after prolongation of œstrogenic treatment is probably due to their metaplasia into fibroblasts.

The prostate reacts to œstrogens in a similar manner. After œstrogen treatment reticulo-endothelial cells appear in the loose areolar tissue around the acini, and with prolongation of the treatment the cells appear to become transformed into fibroblasts and later into fibrous tissue. The fibromatogenic action of œstrogens in the prostate has been recorded in other animals. Zuckerman and Parkes (1936) found that in the monkey œstrone produces increased general fibromuscular growth of the prostate, and Korenchevsky (1941) states that injection of œstradiol dipropionate into castrated male rats produces great fibrous tissue overgrowth, but only a physiological degree of muscular hypertrophy, in the secondary sex organs.

Although the macrophages in the prostate may be formed partly in situ from activation of pre-existing local cells having mesenchymal potencies, the present work suggests that they come mainly via the blood-stream from the spleen and other reticulo-endothelial organs, in which their formation and mobilization is stimulated by œstrogen. This mobilization was observed in animals which received 5 mg. of œstrogen daily for six days or a moderate dose of 0·5 mg. for twenty-eight days. It was particularly marked in the orchidectomized animals in which, even without œstrogenic treatment, the splenic sinuses were dilated and contained many vitally stained macrophages, which were also present in the splenic and hepatic veins. After œstrogenic stimulation for one to three weeks, the number of cells, including vitally stained cells, further increased in the splenic sinuses. When the œstrogenic treatment was prolonged to four weeks, mobilization of the cells

appeared to be accelerated so that the splenic sinuses in the orchidectomized animals became practically empty. The presence of large numbers of vitally stained macrophages in the splenic and hepatic veins of the same animals, however, suggests that the cells were mobilized as soon as they were formed.

The stimulating effect of orchidectomy on the reticulo-endothelial system may be explained by the absence of the neutralizing effect of androgens on œstrogens which are normally found in the male, and probably produced by the suprarenal glands. This neutralizing effect was shown by Ihrke and D'Amour (1931), Browman (1937), and Robson (1938). It may also be due to the stimulating effect of orchidectomy on the anterior lobe of the pituitary, leading to the output of more adrenotropic hormone, which in turn leads to the production of more œstrogen by the suprarenals.

Since the reticulo-endothelial system is an important defence mechanism against malignant tumours in general (Kavetzki and Diadjuscha, 1937; Stern, 1941), the activity of the macrophages should be stimulated in these conditions. The present research indicates that this can be done by the use of œstrogens, under whose influence the tissues, and in particular those of the reproductive system, are provided with numerous macrophages. Moreover, the known fibromatogenic effect of continuous and prolonged œstrogenic treatment, the known genetic relations between macrophages and fibroblasts, and the present findings all point to the probable transformation of macrophages after prolonged œstrogenic treatment into fibroblasts and later into fibrous tissue. This would appear to be the manner in which the beneficial sclerosis occurs in cases of carcinoma of the prostate after endocrine therapy.

The work also shows that orchidectomy stimulates the macrophages, and that the stimulation and mobilization of the cells is accelerated by the combination of orchidectomy and œstrogenic treatment.

Lastly, the present researches point to the desirability of finding a substance allied to œstrogens which possesses a still more powerful stimulating effect on the reticulo-endothelial system without the possible ill effects of œstrogens.

SUMMARY

The effect of various œstrogenic preparations on the reticulo-endothelial organs and on the prostate and uterine horns was studied in 167 vitally stained guinea-pigs, including intact males and orchidectomized and ovariectomized animals.

The results show that œstrogens stimulate the reticulo-endothelial macrophages in the spleen, liver, and lymph-nodes, and that prolonged œstrogen treatment or stimulation by large doses of œstrogen leads to mobilization of the macrophages in these organs and to their accumulation in the secondary sex organs, such as the prostate or uterine horns.

Orchidectomy was also found to stimulate the macrophages, and the stimulation and mobilization of the cells was accelerated by the combination of orchidectomy and œstrogenic treatment. The macrophages in the prostate may be formed partly in situ, but more likely come from the spleen and other reticulo-endothelial organs as a result of œstrogenic stimulation.

Prolonged œstrogenic treatment, particularly in orchidectomized animals, produced marked fibrosis in the prostate, and the findings suggest that this is probably the result of transformation of the macrophages into fibroblasts and later into fibrous tissue, and that this is the manner in which the beneficial sclerosis occurs in carcinoma of the prostate after endocrine therapy.

The stimulation of the reticulo-endothelial system probably increases the general defence of the body against malignant tumours, and the present researches suggest the desirability of finding a substance allied to œstrogens which possesses a still more powerful stimulating effect on the reticulo-endothelial system without the possible ill effects of œstrogens.

In these investigations we gratefully acknowledge assistance from the Central Research Fund of the University of London.

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In Memoriam

SIR HUGH CAIRNS, K.B.E., D.M., F.R.C.S.

(1896—1952)

THE death of Sir Hugh Cairns has come as a sad shock to his many friends all over the world. He died in Oxford on July 18, 1952, after an illness lasting for six months.

Hugh William Bell Cairns was born in Adelaide, South Australia, on June 26, 1896, the only child of a Scottish father and an Australian mother, both of whom have survived him. He was educated at Adelaide High School and in the Medical School of the University, where his training was interrupted by the first world war. After serving in the ranks for a time, he returned to qualify in medicine in 1917, and then obtained a commission in the Australian Army Medical Corps, with which he saw active service in France. His general abilities at his university were recognized by the award of a Rhodes Scholarship, and this brought him to Balliol in 1919, where he read physiology, demonstrated anatomy, and rowed, getting his blue in the Oxford boat of 1920. At Balliol, too, he met the youngest daughter of A. L. Smith, then Master, who was to become his wife. By his entry into this large and gifted family, he acquired relations who were to provide him with much interest and happiness for the rest of his life.

On the termination of his scholarship he became house surgeon to Mr. E. C. Bevers at the Radcliffe Infirmary, and from there he went to the London Hospital in 1921. He got the F.R.C.S. in the same year, and the next few years were spent in house appointments, the pathology department, and as first assistant in the surgical unit. During this period he professed a special interest in genito-urinary surgery, and he was distinguished by his ability for hard work and thoroughness rather than for technical brilliance, but it was these qualities which brought him to the attention of his seniors.

The London was at this time ripe for developments in neurological surgery because Souttar had a special interest in it, and Riddoch knew of the results which were being obtained in Cushing's clinic in America. The Rockefeller Foundation was sympathetic, and so it came about that Cairns went to Boston in 1926, having been appointed supernumerary assistant surgeon at the London and given leave of absence to learn this new specialty. In Harvey Cushing he found the master he could admire unreservedly, and from Cushing he learned the surgical technique, the organization of a clinic, and the system of records which he was to employ so effectively and to hand on to generations of his own pupils. He learned his lesson well and became one of Cushing's favourite disciples. It was an occasion of great satisfaction and happiness for both master and pupil when in 1938 Oxford University conferred the honorary D.Sc. on Dr. Cushing (*see* photograph, p. 174).

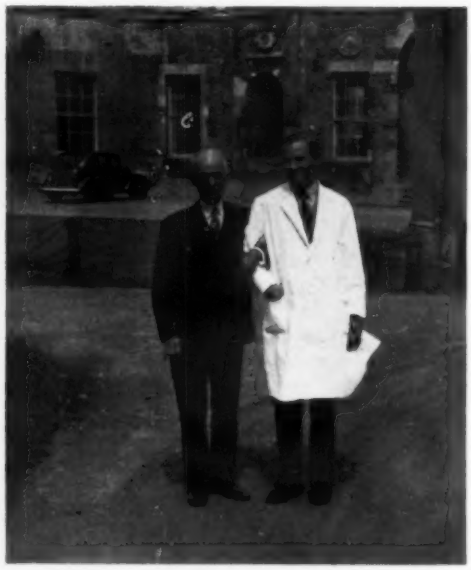
He came back from Boston in 1927 with an assured appointment at the London, but for some time life was not easy. He was a young unknown, doing only neurological surgery, and doing it in a way which seemed highly unorthodox, if not unnecessary, to those in London who were already operating on the brain and spinal cord. His beds were scattered over the vast hospital, there were often difficulties in getting an operating theatre, office accommodation was scanty, assistants were in

SIR HUGH CAIRNS, K.B.E.
1896—1952

irregular supply, nurses had to be trained, and this kind of surgery was not popular with anæsthetists. These were pioneering problems in London, although Jefferson in Manchester and Dott in Edinburgh were establishing the specialty in those centres and meeting the same difficulties. These three men made a school of British neurological surgery of which we have cause to be proud, and each has contributed a particular virtue. Their difficulties are recorded as a matter of historical interest because, in this country at least, they are unlikely to occur again.

But results told, and within a few years Cairns's name was widely known and his professional life became increasingly busy. He simplified his work to some extent by doing all his consulting work at the hospital, but private patients had to be operated on in the West End nursing homes. This division of his labours he always regarded as unsatisfactory, both for himself and the patient. He was one of the first to establish his home away from the conventional residential district for London consultants.

Although he had more than enough to do at the London and in the private nursing homes, he was



Sir Hugh Cairns with Dr. Harvey Cushing at Oxford.

anxious to become identified with the great neurological hospitals, probably because he hoped to establish in London the kind of clinic that he was ultimately to have in Oxford. He was appointed to the Maida Vale Hospital in 1931 and was on the staff for three years, although his work there was chiefly consultative. He missed one appointment at the National Hospital, Queen Square. This was a transient disappointment; he was elected to the staff in 1934, but by this time he was so fully committed at the London that he had little time for other work. He always had a high regard for the National Hospital, and he never missed an opportunity of acknowledging his debt to his neurological colleagues, to Riddoch and Symonds in particular.

Up to this time his career had been similar to that of many successful surgeons—indeed success had come more quickly for him than for many. But he knew that life offered more than mere personal success, and that he himself had more to offer. It was apparent that there was little prospect in London of living and raising his young family close to his work, of doing all his work in one place, and of having some time for study and research. He realized that these problems were by no means unique for his own specialty, and he began to plan a medical school in which the principals would not be subjected to the time-consuming distractions of a busy metropolitan practice. Another visit to Cushing and other influential friends in America in 1935 strengthened his purpose. Although the intricate negotiations which led to Lord Nuffield's benefaction in Oxford have yet to be fully recorded, there is no doubt that Cairns was a vital force in the project, and that his own far-seeing plans determined the course it was to take. His appointment to the Chair of Surgery in 1937 was the natural and wise choice.

He had no qualms about leaving London on personal grounds, and he knew that he was leaving his clinic in the good hands of one of his best pupils. With characteristic thoroughness he took copies of his case records, clinical photographs, and pathological material, and he made much use of them over the years.

His return to Oxford was in a sense a home-coming because there were relatives and family friends, and he knew the Radcliffe Infirmary. The house and garden in Charlbury Road became a centre for his friends, young and old, and he got much happiness from this new life. For the first few months, while the department was finding its feet, there was enough but not too much clinical work. Soon there was a waiting list, and any doubts there had ever been about the adequacy and variety of clinical material were finally dispelled.

He had only 18 months of this comparatively cloudless life in Oxford. The war then absorbed his energies, and during the whole of it he served as consultant neurosurgeon to the Army, rising to the rank of Brigadier. It was through his influence that a special base hospital for head injuries was established at St. Hugh's College in Oxford, and the experience of starting a new clinic at the Radcliffe two years before was of great value in the conversion of St. Hugh's. His opposite number on the medical side was Sir Charles Symonds: they made a powerful team, and it was largely through their efforts that St. Hugh's became a neurological centre of the first importance in which teaching and research went hand in hand with excellent care of battle casualties. Many young neurologists and neurosurgeons owe much of their training to St. Hugh's and will always remember the stimulating atmosphere of the hospital.

At the same time Cairns was busy organizing the mobile neurosurgical teams which were to acquit themselves so well on every front. He was also amassing the clinical, pathological, and experimental evidence which led to the adoption of crash helmets for motor-cyclists in the services, saving an untold number of broken skulls and lives. He had had no great first-hand experience of traumatic cranial surgery, but he threw himself into the routine work of the hospital with characteristic vigour, learning and teaching at the same time. The discovery of penicillin provided another channel for his efforts, and he was quick to realize its enormous importance. He accompanied Sir Howard Florey on a tour of the North African front, conducting clinical trials, and was soon absorbed in determining how penicillin could best be used in the prevention and treatment of cranial and intracranial infections. His work on purulent pachymeningitis and pneumococcal meningitis had immediate results, and was the basis of

the methods of treatment in use to-day. These activities, and others, are recorded in a steady flow of papers which came from his pen during and after the war. He edited the special war supplement of this JOURNAL dealing with head injuries, and it will remain as a valuable contribution to the literature of traumatic surgery.

With all his military commitments he found some time to spare for the undergraduate clinical school which the war had thrust on Oxford, and its welfare remained one of his deepest interests. Through this contact with a civilian hospital he was also able to keep in touch with civilian neurosurgery.

When the war was over he returned to his clinic and was again happy in unhurried clinical work. The demands of administration and official missions made it necessary for him to shed some of his routine work, but this left more time for study and research. His interest in pneumococcal meningitis led on to tuberculous meningitis, and he captained a team which has made contributions of fundamental importance. He was also becoming interested in operations for mental disease and was searching for a more selective procedure than the standard prefrontal leucotomy. He was late to enter this field because he felt that the surgeon must always be the psychiatrist's handmaiden in the selection of cases and assessment of results, and he had spent a good part of his life in equipping himself to deal with ordinary neurological problems from his own resources. He then realized that the neurophysiologist and surgeon had their own contribution to make, and this determined his own approach. He was vastly interested in the operation of hemispherectomy designed by one of his pupils, and at the end of his life was engaged in a characteristically thorough appraisal of the results.

Many honours came his way, but no one ever sought them less. He served on the Council of the Royal College of Surgeons for eight years (1942–50). For his services during the war he was created K.B.E. in 1946. He had been president of the Association of Surgeons of Great Britain and Ireland, of the Society of British Neurological Surgeons, of the neurological section of the Royal Society of Medicine. As the first holder of the Sims Professorship in the Royal College of Surgeons in 1948, he was provided with an opportunity of a visit to Australia, South Africa, and New Zealand, which was in the nature of a triumphal progress for him, being welcomed by old friends and pupils wherever he went. In 1950 he was made an honorary D.Sc. by Northwestern University in Chicago. He gave many eponymous lectures, and he felt none a greater honour than the Victor Horsley Lecture at University College Hospital, which was his last published work. During his last visit to Portugal in April of this year he was made a member of the Portuguese Academy of Arts and Sciences and this ceremony was his last appearance in public.

In addition to his parents, he is survived by Lady Cairns, two sons, and two daughters.

It is not difficult to assess Cairns's stature, even at this sad time. He was essentially good at his work, and his very great natural endowments were given their fullest opportunity by an infinite capacity for hard work. His warm humanity, strength of character, and sound common sense made him a good doctor, but in his specialty he had chosen a life's work which made enormous demands on his physique and morale. He had the dual task of learning clinical neurology and mastering a difficult surgical technique. To read some of his early operation notes is to appreciate an experience almost amounting to anguish : if things went well there was humble satisfaction, and if badly he followed the patient to the autopsy room and made the examination himself, learning something for the next time. His deep concern was obvious to the patient and his relatives and they all knew they had a friend who would give of his best. As time went on and his confidence increased, operating became easier for him, and he could be relied on for a uniform performance—there was none of the *prima donna* about him. Sooner than most surgeons he learned the limitations of his art, and one of the most characteristic features of his practice was that no unnecessary or ill-planned operating was done. There have been more brilliant operators, but in the care of the patient before, during, and after operation, he had no peer.

He had a natural gift for organization and administration, and these qualities contributed much to the success of each of his ventures. As it happened, the Chair of Surgery in Oxford could not have had a more suitable first incumbent, although his own department was concerned with neurological rather than general surgery. He kept abreast of the trends in general surgery and was always keen to pass on developments in his own specialty which might have an application in the general field.

But those who knew him best will remember him as a man of great charm and kindness. Among his pupils he inspired affection and reverence, and it gave him the greatest pleasure to watch their progress. He had many interests outside his profession which he pursued with an amateur's delight and this made him excellent company. Love of music played a very large part in his life : although no performer himself, he had a remarkable ear and memory for music and his family provided a musical background. He had a great admiration for the ballet, and many assistants will remember a sharp rebuke during operations, " It's like the ballet : you've got to keep on your toes ". He was interested in all kinds of sport, and continued to play tennis vigorously until the end of his life ; he went through a phase of enthusiasm for golf and fishing, but only for a brief period before the war was there time for these recreations. He read voraciously and all manner of things ; and this, together with being a good and willing listener, kept him unusually well informed.

To the reader, it may appear that his life showed so many facets that the underlying unity of purpose is not clear. His life *was* complicated, but there was always an objective to be achieved, and he saw it clearly. Although he had accomplished much, he was full of plans for the future when his final illness intervened, and this he bore with the steadfast optimism and courage which had characterized his whole life.

SHORT NOTES OF RARE OR OBSCURE CASES

TORSION OF AN APPENDIX EPIPLOICA OF THE VERMIFORM APPENDIX

By H. J. HAMBURY
ST. JOHN'S HOSPITAL, LEWISHAM

Wakeley and Childs (1949) reviewed the pathology and clinical features of the diseases of the appendices epiploicæ. Beattie (1950) collected 64 cases of torsion of an appendix epiploica, and Rosenbaum and Kissinger (1950) discussed 74 similar cases.

The occurrence of appendices epiploicæ on the vermiform appendix seems to be a matter of doubt. *Gray's Anatomy* (1949) says that appendices epiploicæ do not occur on the rectum, cæcum, or appendix, but Pines, Rabinovitch, and Biller (1941) found them along the whole of the colon including the upper rectum and cæcum, and occasionally on the appendix. *Cunningham's Textbook of Anatomy* (1951) says they occur throughout the length of the large intestine except the rectum, but that they are rudimentary on the appendix. Surgical observation certainly confirms the occurrence of serially arranged fat lobules on the vermiform appendix.

CASE REPORT

Mrs. E. W., aged 34, a housewife, was admitted on Nov. 15, 1951, complaining of abdominal pain of 48 hours' duration. She had had a similar attack one month before,

Fig. 216.—Operation specimen, showing vermiform appendix, with twisted gangrenous appendix epiploica.

which had lasted two days and resolved spontaneously. The pain was all over the abdomen at first, but shifted later to the right side. It was of a dull aching character, of moderate severity, and constant since the onset of the attack. She complained of nausea, but did not actually vomit. She had always suffered from constipation, but it was exceptional that her bowels did not act for three days as was the case since the day before the onset of pain.

On Examination.—She was in good general condition. The tongue was slightly coated and there was some fœtor. Movement of the abdomen on respiration was restricted. There was guarding and tenderness immediately below the umbilicus and in the right iliac fossa. McBurney's sign was positive. There was distinct rebound tenderness in the right iliac fossa. Few bowel sounds were heard. On rectal examination there was tenderness anteriorly and high up, more on the right side than on the left.

A diagnosis of acute appendicitis was made. Appendicectomy was performed immediately and the specimen shown in *Fig.* 216 was removed. No other pathological changes were found in the abdomen. The post-operative course was uneventful and the patient left hospital on the ninth post-operative day. When seen one month after the operation she was perfectly fit and well.

The excised specimen (*Fig.* 216) consisted of the vermiform appendix which was normal except for an infarcted appendage, about $\frac{1}{2}$ in. in diameter, with a tenuous pedicle twisted twice in a clockwise direction. This appendage was attached to the lateral aspect of the mesenteric border at the junction of the middle and distal one-thirds of the appendix. Another appendix epiploica, of similar size but not twisted, was seen nearer the tip. Another one, about $\frac{1}{16}$ in. in diameter, partly congested and partly fibrosed, was seen near the base; it may have been the cause of the attack of pain experienced a month before admission. Thus the serial arrangement of the appendices epiploicæ of the colon was repeated on the appendix.

Patterson (1933), in a careful anatomical and pathological study, suggested that the appendices epiploicæ had a protective function. The vessels of the large gut describe inverted U-shaped loops in the appendices, giving off branches to the respective appendix and to the bowel wall. The appendices are fat pockets protecting the vessels when they become relatively lengthened in the collapsed state of the bowel. The mechanism of torsion is thought by Patterson (loc. cit.) to be due to the fact that the vein is longer than the artery and gradually takes up a tortuous course around it. For reasons of hæmodynamics this arrangement is thought to facilitate torsion. The thickness of the pedicle is not considered relevant. Another factor of importance may be the greater weight of the fat-laden appendix epiploica during digestive plethora, when it is more inclined to twist.

Multiple infarctions of appendices epiploicæ, as a result of thrombosis or torsion, may lead to scar constriction of the bowel. Single infarcted appendices can cause abscess formation or peritonitis, but in most cases the process is innocuous. A curious result of gradual twisting and fibrosis is the detachment of an appendix epiploica; such an event might have taken place soon in the specimen shown if it had not been removed. This process results in the formation of a loose body in the peritoneal cavity, the corpora aliena amylacea described by Littré (1703). Hunt (1919) and Klingenstein (1924) first drew attention to this as a possible mode of formation of peritoneal loose bodies.

I wish to thank Mr. S. H. Wass, under whose care this case was admitted, for constructive criticism and permission to publish these notes.

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'COLLOID' CARCINOMA OF THE PANCREAS

BY E. G. MUIR, LONDON

MUCOID or 'colloid' degeneration is not uncommon in pancreatic carcinoma—in the histological material from 69 cases personally examined traces of such changes were present in 4—but marked 'colloid' change is unusual. In the following case the tumour in the head of the pancreas, though large, was composed almost entirely of 'colloid' material and, though the growth had penetrated the duodenal wall, the common bile-duct was uninvolved.

CASE REPORT

HISTORY.—The patient, a man of 61, had suffered from indigestion for sixteen years and had always supposed that he had a duodenal ulcer. His symptoms had recently become worse, a barium meal showed duodenal deformity, and his physician advised surgical treatment for his ulcer.

Laparotomy on Aug. 28, 1949, revealed a tumour the size of an orange in the head of the pancreas and obviously involving the first and second parts of the duodenum. The common bile-duct was normal in size and there was no evidence that a chronic duodenal ulcer had ever existed. No secondary deposits could be detected and the neck and body of the pancreas were uninvolved by the tumour, though granular and firm as in a 'Banting' pancreas. A pancreatico-duodenectomy was performed with anastomosis of the common bile-duct, the neck of the pancreas, and the pyloric region of the stomach to the first jejunal loop.

PATHOLOGICAL REPORT (Dr. C. F. J. Hall).—The specimen consists of the head and neck of the pancreas with the pylorus and duodenum. The upper part of the head of the pancreas is expanded by a tumour which projects into the duodenum, where it forms an ulcerated mass extending from 2 cm. to 7·5 cm. from the pylorus (*Fig.* 217). There is also a small area of ulcerated growth close to the ampulla of Vater. The latter is not itself involved and the portion of the common bile-duct removed is quite patent. The pancreatic duct is obstructed within the pancreas and its dilatation is marked on the cut surface of the neck. The cut surface of the growth shows much colloid degeneration. The lower part of the head of the pancreas and the neck at the line of excision appear to be uninvolved. One pancreatico-duodenal lymph-node is found.

Section of the growth shows it to be a very well-differentiated adenocarcinoma, which has undergone extreme mucoid degeneration. Section of the cut end of the pancreas shows a subacute pancreatitis, but no evidence of infiltration by growth. The acini are atrophied and distorted, with infiltration of plasma cells and replacement by fibrous tissue. The main duct has lost its epithelial lining and shows cellular infiltration and a little necrosis of its wall. Section of the lymph-node shows marked reactive hyperplasia, but no evidence of metastasis.

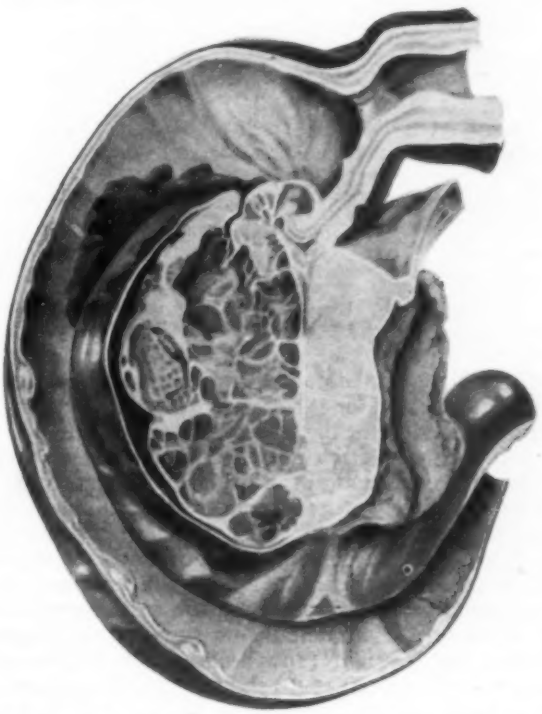

FIG. 217.—'Colloid' carcinoma in head of pancreas with invasion of duodenum.

This patient is now in his third post-operative year. Though this tumour is the largest pancreatic carcinoma I have found possible to excise, he still appears free from recurrence, supporting evidence that 'colloid' degeneration is not necessarily associated with rapid growth, but may occur in growths of low malignancy.

LEIOMYOMA OF THE STOMACH

REPORT OF A CASE PRESENTING WITH REPEATED SEVERE ATTACKS OF HÆMATEMESIS

By MICHAEL N. TEMPEST

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BENIGN growths of the stomach are rare. Eusterman and Senty (1922), after a study of 27 cases of benign gastric neoplasm, concluded that only 1 in 166 gastric tumours is benign. Over a period of five years at the Lahey Clinic, Kiefer (1941) found only 6 cases of benign gastric tumour, whereas 265 proved cases of carcinoma of the stomach were seen.

Benign gastric tumours are important not so much because of their rarity but (1) the severity of symptoms which may occur, (2) the favourableness of their surgical treatment, (3) their liability to undergo malignant change (Maingot, 1948). These points are re-emphasized in a recent paper by Thompson and Oyster (1950).

Leiomyomata are the commonest simple tumours of the stomach. Eliason and Wright (1925) estimate that 60 per cent of all simple gastric neoplasms are leiomyomata, and Minnes and Geschickter (1936) showed that these tumours formed 65 per cent of a group of 522 cases of gastric tumours arising from mesenchyme.

Leiomyomata occur as hard, smooth, round, sessile, or pedunculated tumours. They may project into the lumen of the stomach, remain in the gastric wall, or be attached to the serous surface. Usually single, they vary in size from ¼ in. to 20 in. in diameter. Most benign tumours occur in the pyloric region and arise from the anterior or posterior wall, showing a predilection for the greater curvature.

Histologically these tumours show unstriated muscle-fibres mingled with varying amounts of fibrous tissue: a considerable amount of glandular tissue is often found. Pathological changes may take the form of surface ulceration and degeneration of a colloid, myxomatous, or sarcomatous nature. Eliason and Wright (1925) and, in a later paper, Lahey and Colcock (1940) showed that these tumours are microscopically much less benign than external appearances would warrant. Fortunately, the type of malignant degeneration which occurs in these tumours is usually of a low grade.

Benign tumours of the stomach are usually symptomless unless complicated by bleeding, intermittent pyloric obstruction or interference with gastric motility and secretion. The most striking feature is the tendency to hæmorrhage. Bleeding may vary from a small ooze to a severe hæmorrhage which may be fatal. The resulting anæmia is of the hypochromic iron-deficiency type.

Diagnosis is not easy. Unless large, benign tumours are very rarely palpable, and even at operation, with the stomach readily palpable under direct vision, the differential diagnosis may be difficult (Dewey, 1944). Test-meal analysis is not typical: the only possible exception is in cases of gastric polyposis, which almost invariably show achlorhydria. X-ray examination and gastroscopy are important aids to diagnosis. The criteria for the radiological diagnosis of these tumours laid down by Moore (1924) remain to this day the most complete yet recorded.

CASE REPORT

HISTORY.—C. S., a male brick-labourer aged 31, was first admitted to hospital in February, 1950, as an emergency after a severe hæmatemesis. He stated that since November, 1949, he had felt tired and weak after the slightest exertion. He had been treated by his own doctor for four months for "anæmia": first of all with ferrous sulphate tablets and then with liver injections. Recently he had suffered from frequent attacks of nausea, but never actual vomiting. These attacks were unrelated to meals and were not relieved by antacid powders. At no time had there been any epigastric pain or discomfort. His bowels were perfectly regular but the motions were dark in colour: he assumed that this was due to the iron tablets he was taking.

On admission he was found to be extremely pale. His stools were tarry black and the only other finding on clinical examination was slight epigastric tenderness. Shortly afterwards he had another severe hæmatemesis and his blood-pressure fell to 85/60. A blood transfusion caused a definite improvement, but three days later he had two further attacks of bleeding. His hæmoglobin reading fell to 24 per cent (Haldane standard) red blood-cells 1,910,000 per c.mm.; colour index 0·66. Another blood transfusion was given and his condition steadily improved. He had no further attacks of bleeding and one month later his blood-count was as follows: Hb 80 per cent; red-cell count 5,700,000 per c.mm.; colour index 0·7. In all he had been given 10 pints of blood.

A barium meal was reported on by the radiologist as follows: "Normal-sized stomach, showing normal tone and emptying readily. Coarse rugosity along the greater curvature of the stomach with an incisural defect just beneath the fundus. No other localized defect or ulcerative lesion can at the moment be demonstrated to indicate the site from which the hæmatemesis occurred. No sign of any ulcerative lesion in the duodenum at the moment."

He was discharged from hospital on March 28, 1950, with a provisional diagnosis of hæmatemesis due to peptic ulcer. He remained much improved in health, but his attacks of nausea persisted. In May, 1950, he was readmitted as an emergency after another severe hæmatemesis.

ON EXAMINATION.—He was extremely pale and had fainted after the hæmatemesis. His stools were tarry black in colour and once again the only positive clinical finding was slight epigastric tenderness. He was given two pints of blood and after this his blood-picture was as follows: Hb 46 per cent; red blood-cells 2,220,000 per c.mm.; colour index 1. The differential white-cell count was normal. The bleeding and coagulation times were well within normal limits. Barium-meal examination was repeated and reported on as follows: "Coarse rugosity along the greater curvature of the stomach, suggesting a gastritis, with a large incisural defect just beneath the fundus. The appearance is similar to that shown previously and it has not changed. There now appears to be a small ulcer in the mid-third of the lesser

gastric curvature and it is likely that the large defect in the greater curvature is a spastic effect associated with the former. I am also suspicious of a second site of ulceration higher up in the lesser curvature near the fundus of the stomach. There is no definite lesion to be seen in the duodenum." (*Fig.* 218.)

The filling defect in the greater curvature nevertheless seemed to be too extensive and constant to be explained by a spastic effect. It was thought that the bleeding might be due to portal hypertension and that the filling defect in the fundus of the stomach might be due to extrinsic pressure from an enlarged spleen. The spleen, however, was not palpable and did not appear to be enlarged on percussion. Several liver function tests were carried out, but the results of all were well within normal limits.

FIG. 218.—Barium-meal examination of the stomach. There is a large incisural filling defect in the greater curvature just beneath the fundus. The coarse rugosity along the greater curvature, suggesting a gastritis, can also be seen.

As this was the second time that the patient had been admitted to hospital with severe hæmatemesis, and as the real nature of the lesion was in doubt, laparotomy was decided upon.

AT OPERATION (July 4).—Upper central abdominal incision. There was a large tumour on the anterior wall of the stomach measuring 3 × 2½ in. It encroached upon the lesser curvature of the stomach and protruded well into the lumen of the viscus. There were no enlarged regional glands and the stomach, along with the tumour, was freely mobile. The spleen was normal in size and position. A wide partial gastrectomy was performed, well above the upper limit of the tumour, using an ante-colic valvular type of anastomosis.

PATHOLOGY OF THE SPECIMEN.—

Macroscopical appearance.—On opening the stomach a large solid tumour was seen arising from the upper anterior surface of the stomach and extending on to the lesser curvature. The tumour measured 3 × 2½ × 3 in. and was oval in shape. Most of the tumour was intragastric, but the extragastric portion showed several smooth solid nodules covered by visceral peritoneum, identical in appearance to subserous uterine fibroids. The mucosal surface of the tumour showed one very large ulcer crater, about ½ in. in diameter: its depth was almost 1¼ in. Adjacent to this large ulcer were four smaller ulcerated areas. (*Fig.* 219.)

Microscopical appearance (Dr. H. V. Phelon).—"This is a simple leiomyoma. The ulcers on the mucosal surface appear benign."

FIG. 219.—Photograph of the specimen after partial gastrectomy. The stomach has been opened along the greater curvature. The intragastric portion of the tumour can be seen encroaching upon the lesser curvature. The large ulcer crater shows as a very dark triangular patch, and the smaller ulcers can be seen in the immediate neighbourhood.

PROGRESS.—Following the operation, the patient made a very rapid and uneventful recovery. He was discharged from hospital on July 20, 1950, and when last seen, two months later, was in excellent health.

I wish to thank Dr. L. Glick and Mr. R. W. Hendry, under whose care this patient was admitted, for permission to publish the case; Dr. R. I. Lewis for the radiological examination and reports; Dr. H. V. Phelon for the pathological report; and Mr. K. Greenwood for the photographs.

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EPIPHYSITIS OF THE TUBER ISCHII

By E. N. WARDLE, Liverpool

Since J. M. Berry's article in 1912, something less than a dozen cases have been recorded of a curious condition of the tuber ischii. The patient here presented adds another to the series and has been followed for several years.

Fig. 220.—Radiograph taken 6 months after injury showing a mass of irregular ossified fissure protruding from the left tuber ischii.

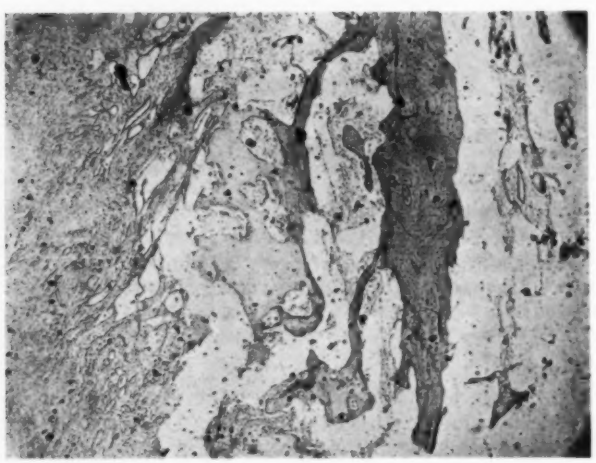

Fig. 222.—Section of mass removed, showing a central island of cartilage flanked by living bone, areas of absorbing bone, and connective tissue. (× 37·5.)

CASE REPORT

S. F., a healthy girl aged 14, was seen in May, 1948, complaining of increasing pain in the left buttock and leg during the preceding six months; she had reached the stage where pain prevented sitting for any length of time. There was a history of a fall from a horse, on to the buttocks, in July, 1947, but the patient had thought little of this and had continued her ordinary activities. Her presenting symptom was a sciatic neuralgia; the presenting sign a hard mass under the lower edge of the left gluteus maximus. The hip-joint was normal. X-ray photograph (*Fig.* 220) showed a calcified hood capping the ischial tuberosity. The child was so miserable from the inability to sit that the tumour was removed. In the lithotomy position an incision was made in the line of the ischial ramus (Milch, 1926): a crescentic mass of calcified material was disentangled with difficulty from the muscular origins; it was quite separate from the ischium, the surface of which showed bare and pitted bone. Convalescence was uneventful. The patient soon resumed her normal life, and is now training as a physiotherapist. Recent radiographs (*Fig.* 221)) show a few isolated spicules of bone and plainly indicate the area where the ischial epiphysis should have been.

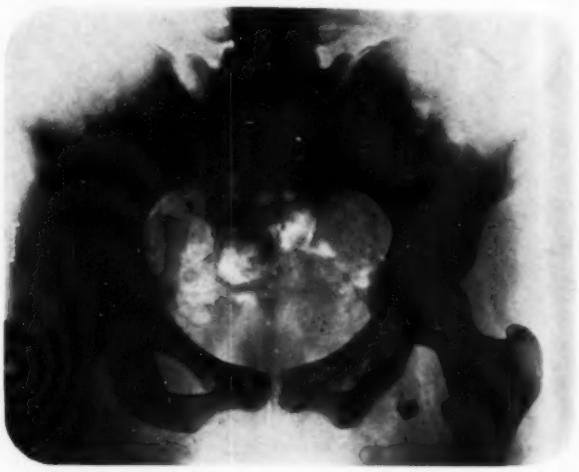

Fig. 221.—Radiograph taken in December, 1951, showing distortion and thinning of the left ischial ramus and a small spicule of bone within the area of the original tumour.

DISCUSSION

Aetiology.—All the cases in the literature have a history of injury—those recorded by Berry (1912), Milch (1926), Hellmer (1933), and Cohen (1937), violent injury shortly before examination; the remainder (Winkler, 1947; Labuz, 1946; McMaster, 1945; and Abbate, 1945), including the present patient, slight injury some time before examination. This probably accounts for the varied titles of avulsion, fracture, and epiphysitis applied to the condition.

Radiological Appearances.—These can be divided into 'new' and 'old'. Films taken shortly after injury show an ill-defined crescentic shadow of uneven density standing off from the tuber ischii. Those taken months or years afterwards reveal an irregular mass of bone. It is difficult to avoid the conclusion that the latter develops from the former and that trauma stands in relation to this condition as it does to slipped upper femoral epiphysis.

Pathology.—Macroscopically the mass of tissue had a hard bony shell and was softer facing the ischium. The ischium itself was bare and pitted; it will be recollected that the normal epiphysis is a thin plate with the centre appearing at about 15 years and joining at 20–25 years; the normal epiphysial cartilage to be expected in this child was missing. Microscopically (*Fig.* 222), the sections showed much dead bone and connective tissue, with islands of living

bone and cartilage. When an epiphysis is separated, whether by trauma or degeneration, or a combination of both, the line of cleavage passes through the metaphysis. The epiphysial centre and cartilage then show changes ranging from very slight to complete necrosis, according to the degree of separation; and regeneration varies in the same way. Slipped ischial epiphysis is suggested as a suitable title for all these cases.

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AN UNUSUAL ISLET-CELL TUMOUR OF THE PANCREAS

BY ISABELLA FORSHALL, P. P. RICKHAM, AND E. G. HALL, LIVERPOOL

THIS case is considered worthy of publication on account of the interesting history and the unusual pathological findings.

CASE REPORT

HISTORY.—B. L., a female child, aged 7½ years, was admitted to Alder Hey Children's Hospital, Aug. 20, 1948.

Two hours before admission the child had slipped in the road while playing and as she fell her abdomen hit the kerbstone. Immediately following the accident she complained of severe pain in the left upper abdomen and appeared to be suffering from shock; she fainted several times and vomited repeatedly. The bowels had not moved since the accident; a small amount of normal urine had been passed.

ON EXAMINATION.—The child was pale, with clammy skin; the pulse was 100 per min. and noted to be thready, temperature 97° F., and respirations 30 per min.; the B.P. was 100/60. She was complaining of pain all over the abdomen. There was fullness in the left upper abdomen, and on palpation a large tender mass could be felt filling the left loin and extending from the left costal margin to the umbilicus; the swelling was dull on percussion. Bowel sounds were present but faint. There was diminished movement of the left chest, but the air entry was good on both sides. No other abnormality was detected.

An hour later the child passed a relaxed stool which contained no blood or mucus. A catheter specimen of urine was normal. The volume of the pulse had improved slightly but the child was still cold, the skin clammy, and the colour poor. A blood transfusion was set up. Four hours after admission the child's condition had sufficiently improved for operation to be thought permissible. A provisional diagnosis of intraperitoneal hæmorrhage, possibly due to ruptured spleen, was made.

AT OPERATION.—The abdomen was opened through a left paramedian incision. There was a small amount of free blood in the peritoneal cavity; a tense purple swelling presented between the stomach and the transverse colon on the left side. It lay behind the peritoneum and extended laterally towards the spleen. The stomach, liver, spleen, left kidney, and intestine were examined, but no intra-abdominal injury was found. The swelling was considered to be a retroperitoneal hæmatoma and the abdomen was closed.

The child made a good recovery following the operation, but the mass in the left upper abdomen remained palpable, though it slowly decreased in size. A straight radiograph of the abdomen and an intravenous pyelogram revealed no abnormality other than a soft-tissue shadow in the region of the original swelling. Full examinations of urine and blood were normal apart from a secondary anæmia. On discharge four weeks after operation the lump was still just palpable. The patient was instructed to attend the Out-patient Department in one month's time, but, in spite of written reminders, she did not attend until twenty months later.

The child turned up in the Out-patient Department on April 18, 1950, and stated that she had been in good health until three months previously, when she had become languid and lost her appetite. There was no complaint of pain or digestive symptoms and no history of fainting attacks.

ON EXAMINATION.—The child was well nourished but pale. There was fullness in the left hypochondrium and on palpation a swelling was felt. It was hard and irregular in outline and almost as big as the child's head; it could, with difficulty, be separated from the left costal margin, gave the impression of being very superficial, and could be displaced forward by a hand in the loin. Directly beneath the costal margin a definite nodule could be felt on the surface of the swelling and the medial aspect presented a notch, rather like the notch of an enlarged spleen. The tumour was dull to percussion and there was no band of resonance over its surface; it could be moved slightly in all directions. No other abnormality was detected.

A straight radiograph showed a soft-tissue swelling in the same position as in the radiograph twenty months before, but much increased in size. A radiograph following a barium meal showed no abnormality in the gastro-intestinal tract, but the stomach was displaced upwards and to the right by the tumour. Radiography of the bony skeleton showed no abnormality. Urinalysis and full blood investigation were non-informative. A slowly growing retroperitoneal tumour was suggested as a pre-operative diagnosis, in spite of the mobility of the mass and the absence of intestine in front of it.

SECOND OPERATION.—A laparotomy was performed on May 8, 1950. The abdomen was opened through a long transverse incision extending from the tip of the 11th left rib, across the midline just above the umbilicus. On opening the peritoneum the tumour presented; it lay beneath the stretched gastrocolic omentum, which had to be dissected from its surface. Thin-walled tortuous dilated veins coursed over the irregular whitish-yellow tumour. Some of these veins were divided, after which mobilization was easily accomplished, revealing a short pedicle consisting of veins and a branch of the splenic artery. The pedicle was dissected free, clamped, and divided, after which it became apparent that the tumour was intimately connected to the tail of the pancreas. The tumour was removed with the tail of the pancreas, the stump of which was oversewn with silk. The abdomen was closed in layers.

The child made a rapid recovery from the operation and has remained in good health.

PATHOLOGICAL EXAMINATION.—

Gross Features (*Figs.* 223, 224).—The tumour measured 17 × 14 × 8 cm., and weighed 1·075 g. The surface

was coarsely lobulated and, except at the point where it was dissected away from the body of the pancreas, covered with a thin film of connective tissue which dipped between the lobules. Running over the surface were numerous large thin-walled veins. The lobules were irregular in size and shape, and for the most part firm

FIG. 223.—External appearance of tumour.

and of uniform pale pink colour. In a few areas the colour was deeper and there appeared to be cysts beneath the surface. On the anterior surface the cut edge noted above formed part of a finely stippled flattened area 5 × 5 cm. which was clearly demarcated from the rest of the tumour. This tissue appeared to be normal

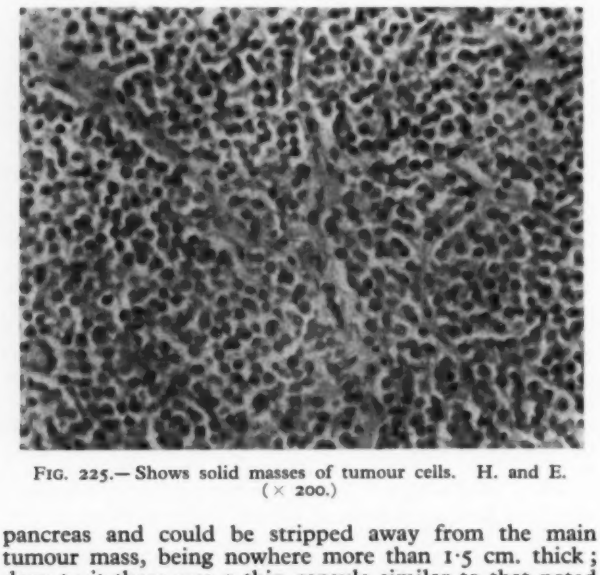

FIG. 225.— Shows solid masses of tumour cells. H. and E. (× 200.)

pancreas and could be stripped away from the main tumour mass, being nowhere more than 1·5 cm. thick; deep to it there was a thin capsule similar to that noted elsewhere.

The main tumour on section was of fairly uniform pinkish-white colour and firm consistency, with scanty pale strands radiating from the centre. There were several areas of hyaline degeneration and patches of hæmorrhage of varying ages, and, at the end posterior to the stretched pancreas, there was much cystic degeneration and hæmorrhage.

Microscopical Appearances.—The pancreatic tissue dissected from the surface of the tumour showed a normal acinar pattern. The islets were prominent, the cells

FIG. 224.—Cross-section of tumour, showing areas of degeneration.

being frequently arranged in ribbons and occasionally showing duct-like structures.

The structure of the tumour varied considerably from place to place. At one extreme it consisted of solid masses of polygonal cells of uniform size, similar to the islets in

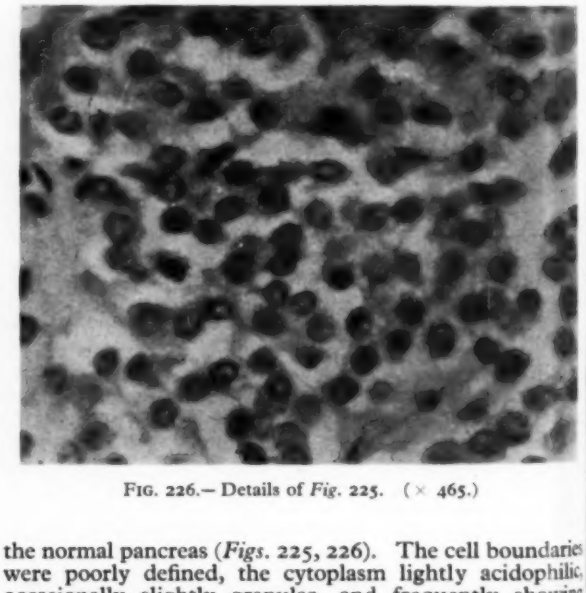

FIG. 226.— Details of *Fig.* 225. (× 465.)

the normal pancreas (*Figs.* 225, 226). The cell boundaries were poorly defined, the cytoplasm lightly acidophilic, occasionally slightly granular, and frequently showing small vacuoles. The nuclei were spherical or ovoid and occupied approximately one half of the cell. Mitoses were not seen. There was a fine chromatin nuclear network slightly denser towards the edges, with an occasional well-defined nucleolus. A proportion of the

nuclei were smaller and stained more deeply ; cytoplasmic inclusions of the type described by O'Leary and Womack were noted. The cell masses were divided into lobules by a fine connective-tissue framework carrying vessels. In their terminal ramifications many capillaries were separated from the tumour cells by endothelium only, but others showed a well-defined perivascular hyaline collar. Red blood-cells were occasionally seen between the tumour cells in clefts devoid of endothelial lining.

At the other extreme and more frequently in the more degenerate parts of the tumour, the cells showed similar features, but many were of columnar type aggregated in

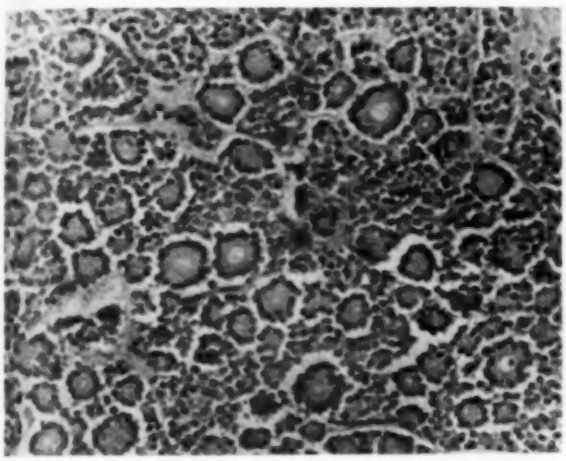

FIG. 227.—Area from part of tumour showing ducts. H. and E. (× 133.)

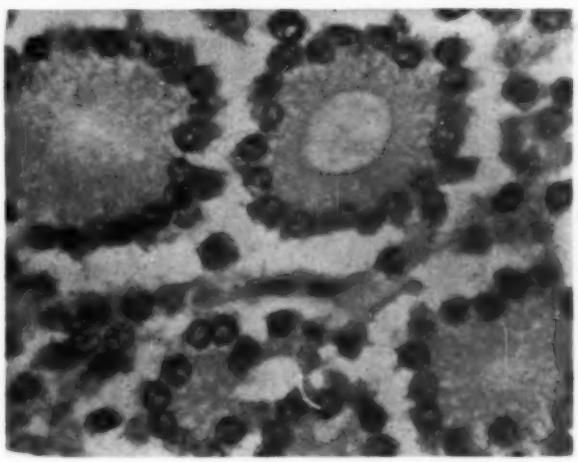

FIG. 228.—Details of *Fig.* 227. (× 465.)

rosettes with basal nuclei occupying about one-third of the cell (*Figs.* 227, 228). In the smaller rosettes hæmatoxylin and eosin preparations frequently failed to show a distinct inner margin to the cells, the cytoplasm of the group being fused, but in the larger rosettes a well-defined lumen was present, either empty or containing amorphous material similar to the cell cytoplasm. Red cells did not occur in this situation. Masson's stain brought out the duct-like nature of these rosettes more clearly, and occasionally showed a pattern of terminal bars between the cells similar to that illustrated by Laidlaw in the ducts of islet-cell tumours. The connective-tissue framework was similar in pattern to that in the solid areas, but usually coarser, and there was frequent hyalinization of the walls of both small and large vessels. Extensive areas showed wide spaces between the rosettes, occupied by degenerate tumour cells and red cells.

Between these two extremes intermediate stages, showing varying proportions of the two types of structure, were seen, often changing abruptly from one pattern to another. In general, the more degenerate areas showed a predominance of ducts, less degenerate ones mainly solid masses of cells. An important variant pattern consisted of solid cords of cuboidal cells, usually two cells thick, running either in an interlacing sinuous manner with blood-spaces between or in parallel trabeculæ separated by delicate capillaries.

Running through the tumour were numerous large vessels often showing hyalinization and fibrosis of their walls. Tumour cells, either singly or in rosettes, were found in the walls and, not infrequently, within the vessels themselves.

Microscopical evidence of degeneration was frequent. In the solid areas intercellular exudate coalesced to form cystic spaces lined by swollen tumour cells, into some of which there had been hæmorrhage. In other areas fibrosis spreading out from the supporting septa to isolate cells was apparent. Though the capsule was in many places extremely thin and showed clumps of tumour cells within it, there was no evidence of spread into the overlying normal pancreas.

DISCUSSION

In retrospect it seems almost certain that the tumour was present at the time of the original injury. The apparently trivial nature of the trauma and the severity of the symptoms might have suggested some underlying pathological condition. The thin-walled tortuous veins on the surface of the tumour would have been easily ruptured, leading to profuse hæmorrhage in and around the tumour. The presence of an adenoma which at the time of the injury was smaller than at the second operation, would be masked by a large retroperitoneal hæmorrhage. Following the first operation the swelling became smaller as the hæmatoma organized and was absorbed, but during the time the child was under observation it never completely disappeared. A great increase in the size of the swelling occurred in the twenty months during which the child failed to attend hospital.

The superficial resemblance of some of the smaller rosettes to the exocrine tissue of the pancreas initially suggested that this might be an adenoma of pancreatic acini. However, more detailed study suggested that its structure was closer to islet than to acinar tissue, a view firmly championed by Professor R. A. Willis. Repeated attempts by several methods to demonstrate zymogen granules gave uniformly negative results in all areas of the tumour ; such granules were easily demonstrated in the overlying normal pancreas. Though some of the smaller rosettes did not show a central canal, the vast majority contained a lumen and resembled the smaller ducts of the normal pancreas. In addition, the cells of the tumour in nuclear and cytoplasmic detail showed a closer affinity with islet than acinar tissue.

Islet-cell tumours show considerable diversity in structure, ranging from solid lobules of polygonal cells to sinuous trabeculated columns and partly tubular areas with columnar epithelium (Isaji, 1939). In some instances ducts are infrequent, and might represent original pancreatic tissue invaded by the

growing tumour (Whipple and Frantz, 1935). In others it appears evident because of number, distribution, close relationship to, or continuity with, islet cells, that ducts may form an integral part of the tumour (O'Leary and Womack, 1934 ; Laidlaw, 1938 ; and others). Indeed, as ducts may occur occasionally in normal islets, and it is known that islet tissue differentiates from duct elements, it is to be expected that such structures would also appear in islet-cell tumours. The tumour we have described shows all gradations from the more typical solid masses and trabeculæ to areas consisting almost exclusively of ducts.

The intimate relationship of vessels and cells which we have described is a feature of the normal islet and of tumours derived from islet tissue. Perivascular hyalinization in mature tumours similar to that detailed above has been emphasized by Laidlaw and by O'Leary and Womack.

Attempts to demonstrate specific granulation in the tumour by the methods of Warren (1938) and Gomori (1939, 1941) were unsuccessful despite secondary treatment with selective fixatives. This may have been due to initial fixation in formol-saline. Alternatively, it is possible that, as this tumour was non-functional, satisfactory initial fixation might not have demonstrated granules. Gomori (1943) stated that 80 per cent of islet-cell tumours are non-functional and that the only one of these subjected to special staining up to the time of his review had shown α-type cells.

It might be suggested that the great size of this adenoma was incompatible with an islet-cell origin. Certainly the vast majority of these tumours are small, but O'Leary and Womack (1934) and Sailer and Zinniger (1946) have recorded pancreatic tumours which were approximately half the size of the present one. That of Sailer was malignant, non-functional, and probably of δ-cell origin.

In view of the histological evidence of capsular and blood-vessel invasion, it is of some significance that, though the tumour was probably present for some time before the accident in 1948, there has as yet been no evidence of metastasis. Frantz (1940) has stressed that in a group of functional tumours showing similar features suggestive of malignancy, there had been no recurrence during an average follow-up period of 4 years, covering a range of 1–10 years.

The definite plane of cleavage between the tumour and the overlying tail of the pancreas suggests that the tumour may have arisen in aberrant pancreatic tissue. It is of interest that Duff and Murray (1942) mention the report by Vecchi of an islet-cell tumour arising in aberrant pancreatic tissue behind the tail of the pancreas.

SUMMARY

A case of non-functioning islet-cell tumour of the pancreas unusual in its size and histological structure is reported. It is possible that the tumour arose in aberrant pancreatic tissue.

We would like to thank Professor R. A. Willis for his comments on the sections.

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AN UNUSUAL CASE OF CROHN'S DISEASE CAUSING ANAL FISTULÆ

BY R. T. BURKITT
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RECTAL manifestations of Crohn's disease are far more common than is usually recognized. These may take the form of intractable anal fistulæ or of recurrent pelvirectal or ischiorectal abscesses. A case of this sort due to Crohn's disease was reported as early as 1934 by Bissell. A high incidence is reported in all subsequent series of Crohn's disease, the highest being that of Jackman and Smith (1943) from the Mayo Clinic. In a series of 114 cases they found as many as 36 cases of anal fistulæ (31·6 per cent). The majority of these, however, were the result of a direct spread from infected crypts of Morgagni. For a fistula to reach the perianal region directly from the small intestine is a rare occurrence, and for this to be the only manifestation of the disease makes the case reported below even more unusual.

CASE REPORT

A. T., aged 52, had always been in good health until December, 1947. He then commenced having persistent pain in the buttock. This was associated with a discharge of mucus, pus, and blood from the rectum. He would complain of gradually increasing pain until he finally "felt something giving way" and then the discharge would occur. Constipation became more and more intractable and the constant pain, the discharge, and the self-performed enemata which he found essential, combined to make his plight a sorry one.

In April, 1949, he attended a hospital for rectal diseases, where a sigmoidoscopy was performed and biopsy taken. The histology revealed nothing specific and the sigmoidoscopic findings were "gross thickening and nodularity of the mucosa especially of the posterior wall up to 12 cm.". A diagnosis of chronic proctocolitis was made and he was discharged.

In February, 1950, he first attended Ashford Hospital, under the care of Dr. K. D. Keele. The condition had been getting gradually worse and the patient's morale was cracking. Apart from a rather peculiar induration on rectal examination, nothing definite could be determined. No evidence of neoplasia could be found and repeated bacteriological examination and other laboratory tests failed to show any evidence of tuberculosis, actinomycosis, lymphogranuloma, or syphilis. Heavy courses of antibiotics, especially aureomycin and streptomycin, produced a temporary improvement, but when discontinued the condition soon relapsed.

In November, 1950, the condition, for the first time, pointed in the right ischiorectal fossa, and an enormous ischiorectal abscess was laid open. The resultant wound gradually healed and for a few weeks the patient felt a little better. Soon, however, pain commenced on the other side and eventually another enormous ischiorectal abscess on this side had to be drained. Colostomy was advised, but for a long time the patient refused. He

FIG. 229.—Diagrammatic sketch of findings at operation, showing fistulous tracks from ileum to peri-anal region.

insisted that his morale had already fallen so low that this final straw would be more than he could stand.

On July 3, 1951, 3½ years after the disease had started, he finally agreed to a colostomy. On exploring the abdomen, a loop of terminal ileum was found to be grossly thickened and to be bound down in the pelvis by a mass of indurated tissue (*Fig.* 229). This was mobilized, and a strictly localized area about 1 ft. in length found to be involved, terminating about 2 in. proximal to the ileocæcal valve. The segment was excised and an end-to-side ileotransverse colostomy performed. In addition it was thought advisable to perform a left iliac colostomy with a long spur to give the sinuses a chance to heal as quickly as possible.

The patient's recovery was dramatic. Within a week all his sinuses had healed, and he was free from pain for the first time in three long years. Three weeks later he left hospital for a convalescent home and now, five months later, his general condition is excellent and closure of his colostomy is to be undertaken.

PATHOLOGY.—

Macroscopical Examination.—The specimen consists of a portion of ileum 20 cm. long attached to thickened fatty mesentery in which are no palpable lymph-nodes. Near one end there are some adhesions with surrounding hæmorrhage and a small hole near the attachment of the mesentery, with slight kinking of the gut. The whole of the serosal surface is inflamed. On opening, the muscle is seen to be much thickened, and the mucosa is granular, ulcerated, and covered with pus in places. At the upper end are four sinuses near the mesenteric border, communicating with the hole seen on the outside, and there is a polypoid protrusion of the mucosa just below. The

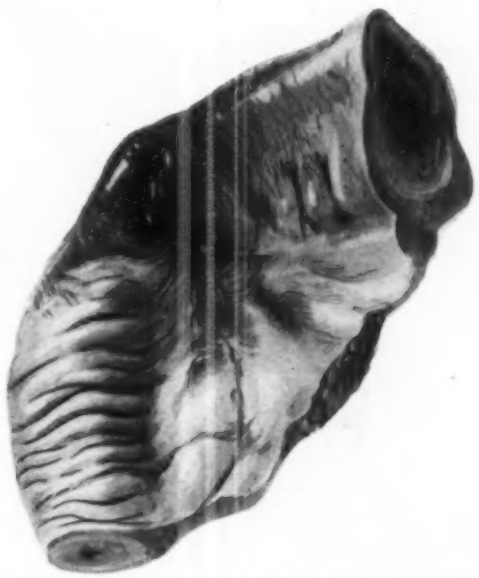

FIG. 230.—Resected portion of ileum, showing kinking at a point of sinus formation.

submucosa is œdematous and the lumen grossly narrowed for the most part, though at the upper end there is relatively normal looking gut. The diagnosis of regional ileitis is highly probable. (*Figs.* 230-232.)

Microscopical Examination.—Sections show that the mucosa is missing over large areas and its place is taken by acutely inflamed granulation tissue. There is inflammation of the whole gut wall, varying in intensity

FIG. 231.—The cut lower end of the specimen to show gross thickening and narrowing of the lumen.

in different parts but tending to be acuter in the serosa than elsewhere. The cells are mainly plasma cells, with lymphocytes and many eosinophils. The muscularis mucosæ is hypertrophic and the submucosa grossly œdematous. The muscular layer is also œdematous and in some places shows considerable fibrosis. All the lymphoid tissue is prominent and large follicles are seen throughout the section, but especially in the submucosa. The germ centres are, however, poorly developed, and

there is no formation of ' tubercles ' or giant cells as is seen in typical Crohn's disease. Professor Hadfield has seen a section and confirms the diagnosis. He states that this is the usual histological picture whenever the ileitis is of long standing and complicated by extensive ulceration.

FIG. 232.—The specimen opened to show the thick walls, ulcerated mucosa, slit-like lumen, and fistulous openings (arrows).

REVIEW OF RADIOLOGICAL EXAMINATIONS.—Radiological examination failed in this case to reveal the true diagnosis. An opaque enema performed in February, 1950, revealed a locally tender mass in the right iliac fossa deforming the rectum and displacing it to the left, which was interpreted as being of inflammatory rather than malignant origin, and associated with the ischio-rectal abscess. The opaque medium could not be forced into the terminal ileum with raised pressure. The subsequent barium-meal examination confirmed these findings. Unfortunately the first film was not exposed until 24 hours after ingestion, when the ileum was empty.

When these examinations were repeated a year later similar findings were noted. A progress film at 6 hours after ingestion was thought to show the meal entirely in the large bowel as far as the rectum, and the absence of delay in the passage of barium through the small intestine unfortunately diverted attention from the ileum. Examination of this film in the light of present knowledge shows what is probably the last 2 in. of the terminal ileum to be smoothly narrowed to a lumen of between 5 mm. and 9 mm., but no true ' string ' sign is present as might be expected to be produced by the degree of narrowing seen in the excised specimen of ileum (*Fig.* 233).

FIG. 233.—Radiograph six hours after barium meal.

This radiological failure in diagnosis is explained by omission of a specific examination of the terminal ileum when routine films had shown no delay therein, and the concentration upon the larger inflammatory condition in the pelvis.

I wish to thank Mr. N. M. Matheson and Dr. K. D. Keele for permitting me to publish the case; Dr. J. A. Brocklebank for the radiological review; Dr. C. F. Ross for the pathological report; Professor G. Hadfield for confirming the diagnosis; and Miss B. Nicholson for the drawings.

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A CASE OF ADENOCARCINOMA OF THE URACHUS SHOWING EXTENSIVE CALCIFICATION

By A. V. POLLOCK, London

Mucoid adenocarcinoma of the urinary bladder is a rare disease. There are two distinct types—those arising in the trigone, presumably in areas of cystitis glandularis cystica, and those presenting in the apex of the bladder and arising from remnants of the urachus. Begg (1931) made an extensive study of urachal remnants and the cysts and carcinomas which arise from them. He described the characteristic mucoid degeneration in these adenocarcinomas and quoted a case of Pendl " in which an enormous tumour the size of an adult head was found, with a capsule in places 2 cm. thick and composed of old sclerosed and avascular fibrous tissue with areas of calcareous deposit ". The case here described shows extensive scattered and lobular calcification and is apparently of a low grade of malignancy.

CASE REPORT

Mr. F. I., aged 46, was referred to the West London Hospital on Oct. 30, 1950, having passed blood-stained urine three days previously, together with some fragments

Fig. 234.—Intravenous pyelogram after evacuation of the bladder. Irregular calcification in a lobulated pelvic tumour.

like tapioca. There was no pain, no increased frequency, and no other symptoms.

The patient had been abroad and had had dysentery in China in 1925. He had been treated for a duodenal ulcer since 1936 and had to take care with his diet.

He looked very fit and general examination showed no sign of disease except in the abdomen, where a hard mass was felt in the midline below the umbilicus deep to the abdominal muscles. It was 11 cm. in length and 8 cm. in breadth and was moderately mobile and not tender.

The urine was completely clear and sterile on culture. Microscopical examination showed a few red blood-cells. Radiographic examination with intravenous diodone showed a large calcified tumour in the pelvis pressing on but not apparently arising from the bladder (*Fig.* 234). Both kidneys functioned normally and their pelvic outlines were normal.

Cystoscopy was performed under general anæsthesia The bladder neck, ureteric orifices, and trigone were normal. There was no cystitis. On the vault above the right ureteric orifice was a shadow-casting projection the

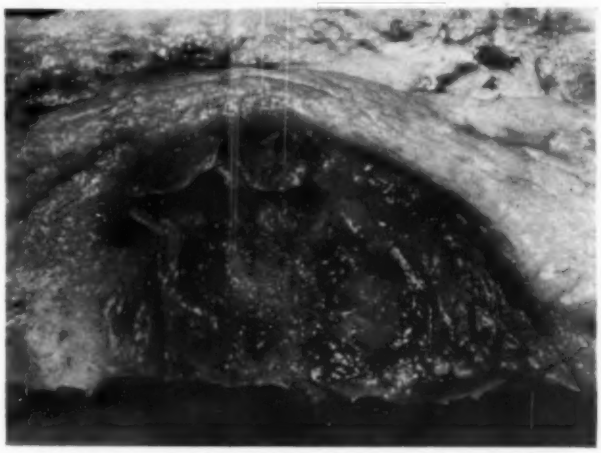

Fig. 235.—Vesical aspect of the posterior half of the tumour cut coronally. The glistening warty appearance of the tumour contrasts with the surrounding normal bladder mucosa. (× 2·375.)

Fig. 236.—Radiograph of the excised tumour, showing scattered and lobular calcification.

surface of which was glistening and warty and not covered by normal vesical epithelium (*Fig.* 235).

A pre-operative diagnosis of calcified extravesical neoplasm invading the bladder was made and an operation was performed by Mr. G. F. Grant Batchelor on Nov. 20, 1950. The tumour was found deep to the rectus muscles. It was cigar-shaped, extending from

the apex of the bladder, which was invaded over an area about 1 in. in diameter to the umbilicus. The underlying peritoneum was involved but no intraperitoneal spread had occurred. The tumour, together with the peritoneum and bladder wall, was easily resected, and the wound

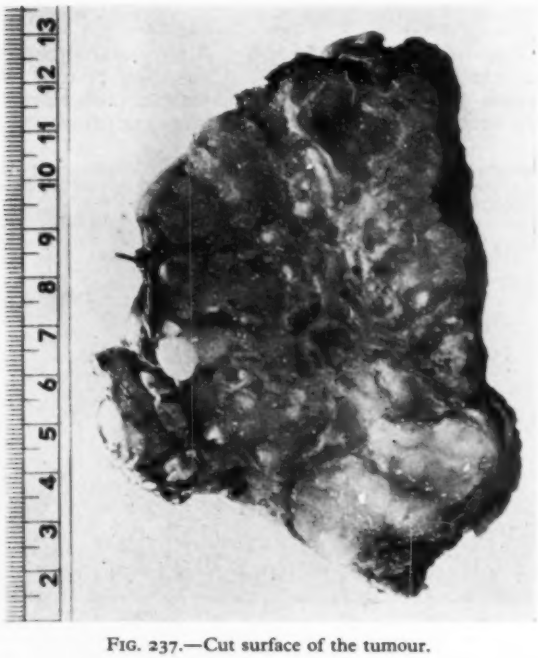

FIG. 237.—Cut surface of the tumour.

closed. The bladder was drained by an indwelling urethral catheter for five days and healing occurred by first intention.

THE SPECIMEN.—Radiography of the specimen showed extensive scattered calcification (*Fig.* 236). I am indebted to Dr. R. G. Waller for the following report: "The specimen is a lobulated tumour measuring approximately 4 in. by 3 in. by 2¼ in., to which is attached a portion of the wall of the bladder. The cut surface shows fibrous septa enclosing masses of mucoid degenerating material with some areas of calcification (*Fig.* 237). Microscopically the tumour is a columnar-celled adenocarcinoma showing extensive colloid degeneration (*Fig.* 238). The tumour is extending to, but does not appear to have ulcerated, the mucosa of the bladder. The appearances suggest a urachal adenocarcinoma."

FOLLOW-UP.—On Dec. 12, 1951, the patient was in good health and free from symptoms or signs suggestive of recurrence. Microscopical examination of the urine showed no abnormality, the blood-urea was 24 mg. per 100 c.c., cystoscopy showed a normal bladder apart

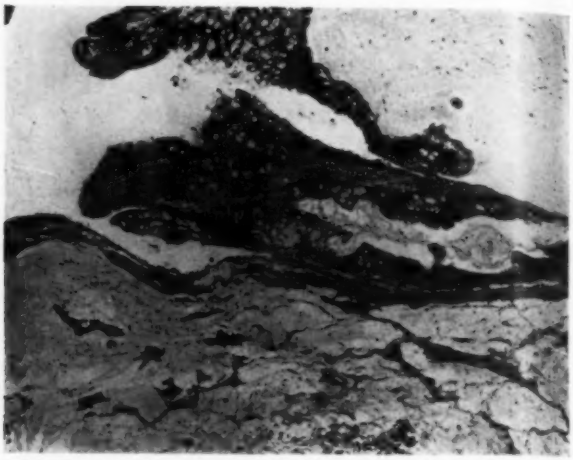

FIG. 238.—Photomicrograph. Mucoid degenerating adenocarcinoma of the urachus. (× 40.)

from a well-healed scar on the vault, and intravenous pyelography showed no abnormality of kidneys or ureters and no abnormal calcification.

DISCUSSION

Hurwitz, Jacobson, and Ottenstein (1951) reported the fifty-fourth case of urachal carcinoma in the literature. Hayes and Segal (1945) gave a valuable review of 45 cases and concluded that the tumour occurs only in adults, is variable in its degree of malignancy, and responds poorly to irradiation. The present case is the only one in the literature to show extensive calcification.

I am indebted to Mr. G. F. Grant Batchelor for permission to report this case.

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REVIEWS AND NOTICES OF BOOKS

Diseases of the Ear, Nose and Throat. Edited by W. G. SCOTT-BROWN, C.V.O., M.D., F.R.C.S., Ear, Nose, and Throat Surgeon, Royal Free Hospital, London. In two volumes. Vol. I. Pp. 756 + xv, with index, 338 illustrations, and 19 coloured plates. Vol. II. Pp. 639 + xv, with index, 260 illustrations, and 8 coloured plates. 1952. London: Butterworth & Co. (Publishers) Ltd. £8 8s. per set.

THIS comprehensive work in two large volumes represents the effort of numerous contributors from this country and from overseas. Each contributor has been chosen because of his special interest in the subject concerned. These authorities have between them covered the whole field of the many and varied conditions which are met with in the diseases of the ear, nose, and throat. There can be no doubt that the practical, balanced survey of all the major advances in this branch of surgery has been planned to meet several needs.

The two volumes are extensively illustrated with excellent clinical pictures, radiographs, and photomicrographs which give to the work a sense of completeness in design and effort.

Throughout the whole work methods of investigation, procedure, and diagnostic principles are clearly presented for the benefit of the general practitioner. The specialist will find that rare conditions as well as the more usual diagnostic problems are discussed, while treatment, including operative procedures, is dealt with in a lucid way and in considerable detail.

As a rule, when many contributors make up a work such as this there is a considerable overlap of material and some disjointedness of style but neither of these conditions is to be found in these volumes.

An excellent production and worthy of British surgery.

The 1951 Year Book of Neurology and Psychiatry (November, 1950—October, 1951). Edited by ROLAND P. MACKAY M.D., and NOLAN D. C. LEWIS, M.D. 5½ × 7⅝ in. Pp. 556, with 109 illustrations. 1952. Chicago: Year Book Publishers Inc. $5.50.

THIS year, articles on the surgery of the nervous system have been incorporated in the sections of neurology and psychiatry, edited respectively by Dr. R. P. Mackay and Dr. N. D. C. Lewis, and regret will be felt that Dr. Percival Bailey, through pressure of other duties, has had to resign his editorship of a special section on neurosurgery which has characterized past issues of this book. Articles on tumours of the brain and spinal cord, however, appear in the section on neurology and are of particular interest to the surgeon. Extramedullary gliomatous tumours within the spinal theca in the lumbosacral region reported from the Mayo Clinic, it is suggested, may arise by neoplastic change in heterotopic 'pinched off' glial tissue. A lymphocytoma causing spinal block in an infant aged 5 months is quoted from an article reviewing 23 cases of intraspinal tumours diagnosed during the first year of life. As perhaps might be expected, consideration of the epilepsies, about which there is so much that is still controversial, require a good deal of space, and some 33 pages are taken up with reports concerning them. As an indication of some of the other material of this compendium, the following may be cited, Diagnostic and Therapeutic Methods, Child Psychiatry, Vascular Disturbances, Degenerative Diseases. To neurologists and those primarily interested in the nervous system this yearly review is what our own MEDICAL ANNUAL is to so many practitioners and others who work in wider fields, and the gleamings from the 1951 harvest will be found to be abundant.

Portrait of a Hospital, 1752–1948. To commemorate the bi-centenary of the Royal Infirmary, Manchester. By WILLIAM BROCKBANK. 6½ × 9¼ in. Pp. 217 + x, with Frontispiece, 56 Illustrations, and 3 Maps. 1952. London: William Heinemann Ltd. 25s.

IT is interesting to read that the bi-centenary of the opening of the "Publick Infirmary at Manchester" falls on July 27, 1952. Dr. Brockbank has written a most fascinating account of the work of the Manchester Royal Infirmary during the last two hundred years. This period of time has seen great advances in all branches of medicine and surgery, and the staff of this great institution have played their part in no uncertain way in helping these advances. When it is considered that the population of Manchester was twenty-two thousand in 1773 and seven hundred thousand in 1948 it will be understood that the original hospital was too small to cope with the ever-increasing population of Manchester.

Dr. Brockbank traces the history of the infirmary, which was closely associated with the lunatic-hospital, down the two hundred years and gives an account of the destruction of the new building in 1940. Since the end of the second world war not only rebuilding but extensions have taken place, notably in the department of neurology and neurosurgery, involving the building of a new operating theatre block, with a radiological unit equipped with all the modern devices necessary for the X-ray investigation of diseases of the nervous system.

Dr. Brockbank has proved himself an able historian, and his interest not only in the hospital but Manchester in general has been portrayed in this book.

The reader is given a very vivid picture of the poverty, disease, and degradation which was rife in the Manchester area two hundred years ago.

We want to know more about the early history of our hospitals up and down the land and Dr. Brockbank has given us an example as to how these data can be presented.

Careers in Medicine. By Various Authors. Edited by P. O. WILLIAMS, M.A., M.B., B.Chir., M.R.C.S., L.R.C.P. With a Foreword by DENIS BRINTON, D.M., F.R.C.P., Late Dean of St. Mary's Hospital Medical School. 5¼ × 8 in. Pp. 265 + xx. 1952. London: Hodder & Stoughton. 15s.

THIS is a most useful book and it fulfils a real want at the present time. There is no authoritative guide at present to the embryo would-be doctor. It will also prove a ready reference volume to the innumerable parents who are considering the medical profession for their sons and daughters, for it gives just that information that they find so hard to obtain elsewhere. It is an insight of the many and varied branches of medicine. One of the fascinating aspects of medicine is the diversity of ways in which it may be practised. Within the profession there is room for all blends of skill; it is truly both an art and science, giving scope to the philosophical, analytical, and mechanical mind.

Dr. D. H. Brinton writes an excellent Foreword to this book and he considers that the plan for the book is a good one.

The contents of the book are divided into three parts: Part I includes pre-clinical studies of anatomy, biochemistry, physiology, and pharmacology. Part II deals with the clinical curriculum in a practical and interesting way. Many contributors have written fascinating chapters. Part III is concerned with the post-graduate work and the various forms of practice that are open to the qualified doctor.

A most useful book.

Logan Turner's Diseases of the Nose, Throat, and Ear. Edited by DOUGLAS GUTHRIE, assisted by JOHN P. STEWART. Fifth edition, completely revised. 5⅝ × 8¾ in. Pp. 478 + xvi, with 246 illustrations and nine coloured plates. 1952. Bristol: John Wright & Sons Ltd. 42s.

THE Edinburgh oto-laryngologists are to be congratulated on having the wisdom to re-edit Logan Turner's well-known text-book.

Although the new edition has been entirely re-cast and re-written it still savours of Logan Turner and we should like to thank the Edinburgh team of specialists for their work and labour of love.

The new edition contains some excellent illustrations, 246 in all, and 9 coloured plates. These in themselves help to enhance the value of this book.

A. Brownlie Smith has contributed an excellent section on the sulphonamides and the antibiotics in the treatment of infections of the ear, nose, and throat.

We predict that this new edition will be as popular as the former ones and that it will be read by students and practitioners not only north of the border but by those in the south as well.

The volume is a real memorial to the name of Logan Turner.

Surgery of the Chest. (*A Handbook of Operative Surgery.*) By JULIAN JOHNSON, M.D., D.Sc. (Med.), Professor of Surgery, School of Medicine and Graduate School of Medicine, University of Pennsylvania; and CHARLES K. KIRBY, M.D., Assistant Professor of Surgery, School of Medicine, University of Pennsylvania. 5⅛ × 8¼ in. Pp. 387, with a large number of illustrations. 1952. Chicago: Year Book Publishers, Inc. (London: Interscience Publishers Ltd.) 68s. (60s. if subscriber to whole series.)

THIS is in reality a handbook of operative surgery dealing with the thorax. It gives the pre-operative and post-operative treatment of chest conditions and a detailed description of the various operative procedures. The monograph is illustrated by some eighty-one plates which depict various operations. These plates are of great value to the reader, but it is a pity that legends are not inserted below the drawings. It is true that a full description of the drawings is given in the text, but so often this is not on the page opposite the drawing.

The various operations of the heart, lungs, œsophagus, diaphragm, and great vessels are all well described and illustrated. This book should prove of real value to those surgeons who have a background of general surgery and wish to become *au fait* with the various thoracic surgical procedures. It will prove invaluable to those post-graduate students who are studying for higher surgical diplomas or degrees.

Surgical Papers by William Stewart Halsted. Edited by WALTER C. BURKET. In two volumes. 7 × 10 in. Vol. I. Pp. 586 + xliv. Vol. II. Pp. 603 + viii. Baltimore: The John's Hopkins Press. (London: Geoffrey Cumberlege.) 200s.

THE surgical papers of William Halsted fill two large volumes, and these various papers may be said to cover the whole field of surgery. It is given to very few surgeons to have such an extensive surgical experience. It is surprising that, although Halsted died in 1922, yet his writings cover the fields of plastic surgery, surgery of the chest, and the surgery of the thyroid, parathyroid, and thymus glands.

It is fitting that these volumes should contain an appreciation of Halsted by Dr. Rudolph Matas which he delivered on the occasion of the memorial meeting held at Homewood in December, 1923.

It may well be said that no surgeon of modern times has had the experience of Halsted, because to-day surgery is fragmented and new special branches seem to spring up each year. Halsted surveyed the whole field of surgery and there was no branch in which he did not enter.

Halsted's papers, which include a vast amount of clinical cases, make fascinating reading, for in them one sees the beginning of modern surgery as we know it to-day.

Surgeons the world over should read these volumes, for in them they will not only gain experience but also inspiration.

The Johns Hopkins Press have performed a great service to surgery as a whole in publishing the papers of this great American surgeon.

Surgical Forum. Proceedings of the Forum Sessions, Thirty-seventh Clinical Congress of the American College of Surgeons, San Francisco, California, November, 1951. By Surgical Forum Committee (Editor: Owen H. Wangensteen, M.D., F.A.C.S.) 6¾ × 9¾ in. Pp. 667 + xxxiv, with 290 illustrations. 1952. Philadelphia and London: W. B. Saunders & Co. 50s.

THIS large volume contains the proceedings of the Forum sessions of the thirty-seventh clinical congress of the American College of Surgeons which was held at San Francisco in November, 1951. Dr. Wangensteen and his colleagues have certainly produced a most interesting volume, embodying a large amount of surgical research which has been carried out in the various hospitals and clinics throughout the United States.

The volume indicates that the modern surgeon, besides being a skilled surgical technician, must also have a good sound knowledge of biochemistry.

The numerous articles which go to make up this volume cover the whole field of surgery, and much of the material deals with experimental surgery performed on animals. It is interesting to read that the main pulmonary artery in dogs can be permanently ligated and the cardiac output diverted through an extracardiac shunt of plastic tube and homologous vein graft. Normal dogs tolerate the procedure well and physiologically the shunt closely simulates the normal pulmonary artery.

The effects of cortisone on skin transplants in the experimental animal reveal the fact that retardation of the fibrocytic response occurs.

The whole volume is full of stimulating ideas, some of which are proved or disproved by the experimental method.

Transactions of the Twenty-fifth Meeting of the Northern Surgical Association. Held in Copenhagen, June 27–29, 1951. 6¼ × 9¾ in. Pp. 460 + xvi. 1951. Copenhagen: Ejnar Munksgaard. 26s.

A WIDE range of subjects was discussed, and only a few of these have been selected for review.

Moberg, of Goteberg, Sweden, opened a discussion on the surgery of the hand in a paper which reflected the present practice in Britain. As he pointed out, it is not possible for all patients suffering from tendon injuries to be treated in special centres, particularly in countries with a widely scattered population, and it is therefore important that the general surgeons be thoroughly conversant with the recent developments in the field of hand surgery.

In a discussion on the follow-up results of patients suffering from carcinoma of the stomach, and treated by thoraco-abdominal operations, two interesting contributions came from Holst's clinic in the University Hospital in Oslo. In the four years 1946–50, 125 patients were treated in this way. The majority were treated

by total gastrectomy, but in a small group the cardiac end of the stomach was resected. The overall mortality was 13·2 per cent. Over 90 per cent of the patients had post-operative troubles of one kind or another, regurgitation, pain, or difficulty in swallowing being the principal complaints. Only 6·7 per cent were able to do a full day's work and none treated by total gastrectomy had regained his pre-operative weight. The treatment indeed is sometimes worse than the disease. It was suggested that if possible a rim of stomach should be preserved at the cardia. For cardiac growths an upper gastric resection seemed to be associated with less regurgitative symptoms than total gastrectomy, and was recommended.

A discussion on the treatment of achalasia of the cardia showed that Scandinavian surgeons had a less favourable experience of Heller's operation than British surgeons. This difference in results was attributed to an inadequate length of the incision in the œsophageal wall. Several surgeons reported unsatisfactory results from cardioplasty, the usual cause being regurgitation through an incompetent cardia, with consequent œsophagitis. There was a general inclination to return to the Heller type of operation.

One of the features of the meeting was a symposium on the subject of carcinoma of the breast. Dahl-Iversen, of Copenhagen, advocated increase in the scope of the radical operation. He advised clearance of the supraclavicular nodes, because in 33 per cent of patients with axillary lymph-node involvement there is also spread to the supraclavicular glands. He recommended also the clearance of the parasternal nodes in view of the findings of Handley and Thackray. In order to facilitate the dissection of the lymphatic channels a pre-operative injection of a blue dye was made into the four quadrants of the breast. This extended operation had been carried out in 100 patients but sufficient time had not elapsed to allow assessment of the survival periods.

Rosenquist, of the Karolinska Hospital, Stockholm, advocated pre-operative irradiation in which 1500 r were given, followed one month later by the classical radical operation. After operation a further course of radiotherapy was given, 3000 r being administered. In a careful and critical appraisal, Rosenquist rejected McWhirter's method of treatment until ten-year follow-up results are available, particularly as the results from his own series of 1014 patients from the Karolinska Hospital were better than the most recent Edinburgh figures. The five-year survival figures were: for Stage I cases 79·1 per cent, and for Stage II cases 46·6 per cent.

Several papers reported the use of resection in the surgical treatment of pulmonary tuberculosis. It was apparent that the indications for the employment of resection were being extended, and it was now sometimes used in the case of upper lobe cavities without preceding collapse therapy. However, the consensus of opinion favoured the trial of collapse surgery before proceeding to resection.

There were two reports concerning valvulotomy for mitral stenosis. Husfeldt, of Copenhagen, reported 28 patients with 6 deaths. Of the 7 patients who had heart catheterization performed before and after operation 6 showed a considerable reduction in the pulmonary arterial pressure; 10 patients were examined from 5½ to 18 months post-operatively, and, of these, 6 were without symptoms and at full work; 3 patients were working with some difficulty and 1 was unable to work.

It was evident in the discussion on rectal surgery that Scandinavian surgeons had been greatly influenced by the teachings of the St. Mark's school, and for the most part the techniques described were in accord with British opinion.

Among the many interesting short papers was one by Foged and Koster (the name of the latter will be familiar to surgeons who served in 21st Army Group in the last war) describing the results of partial amputation of the foot in the treatment of gangrene associated with diabetes.

One of the results of the last war has been the increasing tendency of Scandinavian workers to record their contributions in the English language, and study of the transactions of this meeting shows the high standard of surgical work in these northern countries.

The Foot. By NORMAN C. LAKE, M.D., M.S., D.Sc. (Lond.), F.R.C.S. (Eng.), Senior Surgeon and Director of Surgical Division, Charing Cross Hospital; etc. Fourth edition. 5½ × 8½ in. Pp. 466 + vi, with 166 illustrations. 1952. London: Baillière, Tindall & Cox. 25s.

THIS popular and interesting monograph on the foot has now appeared in a fourth edition. The new edition has been completely revised and much new matter has been added, with some thirty new illustrations.

There can be no doubt whatever that Mr. Lake has written the best book on the foot, because it contains everything dealing with the evolution, anatomy, physiology, and diseases of the foot in theory and practice.

This book will remain the reference volume concerning the foot for many years, and will be consulted both by student and practitioner, while the general surgeon will find in it much that he cannot find elsewhere.

BOOK NOTICES

[The Editorial Committee acknowledge with thanks the receipt of the following volumes. A selection will be made from these for review, precedence being given to new books and to those having the greatest interest to our readers.]

The Clinical Application of Antibiotics (Penicillin). By M. E. FLOREY, M.D., from the Sir William Dunn School of Pathology, Oxford. 6 × 9¾ in. Pp. 730 + xiv, with 115 illustrations. 1952. London: Oxford University Press. 84s.

After-treatment. A Guide to General Practitioners, House Officers, Ward Sisters, and Dressers in the Care of Patients after Operation. By H. J. B. ATKINS, D.M., M.Ch (Oxon.), F.R.C.S. (Eng.), Surgeon and Director of the Department of Surgery, Guy's Hospital. Fourth edition. 5⅝ × 8¾ in. Pp. 338 + xviii, with 64 illustrations. 1952. Oxford: Blackwell Scientific Publications. 30s.

Prostatectomy. A Method and its Management. By CHARLES WELLS, Professor of Surgery, The University of Liverpool. 6⅛ × 9⅞ in. Pp. 103 + viii, with 72 illustrations. Edinburgh: E. & S. Livingstone Ltd. 24s.

The Treatment of Injuries to the Nervous System. By DONALD MUNRO, M.D., F.A.C.S., Surgeon-in-Chief, Department of Neurosurgery, The Boston City Hospital; etc. 6¼ × 9¼ in. Pp. 274+ xvi, with 47 illustrations. 1952. Philadelphia and London: W. B. Saunders Co. 37s. 6d.

An Introduction to Abdominal Diagnosis. A Handbook for Students and Practitioners. By ALAN E. LEE, M.D. (Melb.), F.R.C.S. (Eng.), F.R.A.C.S., Senior Visiting Surgeon, Brisbane Hospital, Brisbane. 5⅞ × 9⅛ in. Pp. 176. 1951. Sydney: Australasian Medical Publishing Co. Ltd.

Osteoarthritis of the Hip. By W. ALEXANDER LAW, O.B.E., M.D., F.R.C.S., Assistant Surgeon, Orthopædic Department, the London Hospital; Associate Surgeon the Robert Jones and Agnes Hunt Hospital, Oswestry; Orthopædic Surgeon, Tilbury and Riverside Hospital; Consulting Orthopædic Surgeon, the Charterhouse Rheumatism Clinic. 5⅜ × 8½ in. Pp. 87 + xii, with 31 illustrations. 1952. London: Butterworth & Co. 25s.

Psychosurgical Problems. By the Columbia Greystone Associates. Second Group. Edited by FRED A. METTLER. M.D., Ph.D., Sc.D. 6¼ × 9¼ in. Pp. 357 + xii, with 56 illustrations. 1952. London: Routledge & Kegan Paul Ltd. 42s.

Synopsis of Genitourinary Diseases. By AUSTIN I. DODSON, M.D., F.A.C.S., Professor of Genitourinary Surgery, Medical College of Virginia, etc., and DONALD L. GILBERT, M.D., Instructor in Urology, Medical College of Virginia. 4¾ × 7¼ in. Pp. 313, with 122 illustrations. 1952. London: Henry Kimpton. 30s.

The Spread of Tumours in the Human Body. By R. A. WILLIS, M.D., D.Sc. (Melbourne), F.R.C.P. (London), Professor of Pathology in the University of Leeds; formerly Pathologist to the Alfred Hospital, and to the Austin Hospital for Chronic Diseases, Melbourne. 6½ × 9⅝ in. Pp. 447 + x + 28-p. Index, with 85 illustrations. 1952. London: Butterworth & Co. 63s.